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(54) Title: NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract: The present invention provides polynucleotides and secreted proteins encoded by the polynucleotides. The proteins include a variety of fusion proteins, including fusions comprising a signal peptide selected from the group consisting of signal peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide. The invention further provides therapeutic and diagnostic methods utilizing the polynucleotides, polypeptides, and antagonists of the polypeptides.



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Description

NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

BACKGROUND OF THE INVENTION

Within the field of genetic engineering, polynucleotides encoding proteins of interest have been identified and cloned by methods that require a detailed knowledge of the structure and/or function of the polynucleotide or the encoded protein. These methods include hybridization screening, polymerase chain reaction (PCR), and expression cloning.

With the more recent advent of large DNA sequence databases and the accompanying data analysis tools, identification of genes of interest is possible through the analysis of raw sequence data. Databases can be "mined" to locate sequences that resemble (are "homologous to") sequences of known function. Alignment of similar sequences can be used to place novel sequences within families of structurally similar sequences. These analytical tools can be combined with structural information obtained from, for example, X-ray crystallography to predict the higher order structure of a novel polypeptide. These analyses also facilitate prediction of polypeptide function. These recent technological advances have greatly increased the pace of gene discovery.

Genetic engineering has made available a number of genes and proteins of pharmaceutical or other economic importance. Such proteins include, for example, tissue plasminogen activator (t-PA) (U.S. Patent No. 4,766,075), coagulation factor VII (U.S. Patent No. 4,784,950), erythropoietin (U.S. Patent No. 4,703,008), platelet derived growth factor (U.S. Patent No. 4,889,919), and various industrial enzymes (e.g., U.S. Patents Nos. 5,965,384; 5,942,431; and 5,922,586).

Although estimates vary as to the amount of the human genome that has been identified to date, there remains a need in the art for further characterization of the human genome and the proteins encoded thereby. Previously unknown genes and proteins will be useful in the treatment and/or prevention of many human diseases, included diseases that have heretofore been refractory to treatment.

35 SUMMARY OF THE INVENTION

Within one aspect of the invention there is provided an isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as

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shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422. Within one embodiment, the isolated polypeptide is from 15 to 2235 amino acid residues in length. Within another embodiment, the at least fifteen contiguous amino acid residues of SEO ID NO:M are operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEO ID NO:423. Within another embodiment, the polypeptide comprises at least 30 contiguous residues of SEQ ID NO:M. Within a further embodiment, the polypeptide comprises at least 47 contiguous residues of SEQ ID NO:M. Within additional embodiments, the polypeptide is selected from the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, and 416; or the group consisting of polypeptides of SEQ ID NOS: 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, and 416.

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Within a second aspect of the invention there is provided an isolated, mature protein encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421. Within certain embodiments, N is 3, 5, 7, 9, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 81, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 135, 137, 139, 155,

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157, 161, 163, 165, 167, 173, 177, 179, 185, 201, 203, 205, 207, 209, 223, 229, 231, 233, 235, 239, 241, 249, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 309, 311, 313, 315, 321, 323, 327, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, or 415; or N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.

A third aspect of the invention provides isolated polynucleotides 20 encoding the polypeptides disclosed above. Within certain embodiments of the invention the polynucleotides comprise a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer as defined above

Within a fourth aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a 25 DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and a transcription terminator. Within certain embodiments, M is 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42,

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48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, or 416; or M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.

A fifth aspect of the invention provides a cultured cell comprising the expression vector disclosed above. The cultured cell can be used, *inter alia*, within a method of producing a polypeptide, the method comprising (a) culturing the cell under conditions whereby the sequence of nucleotides is expressed, and (b) recovering the polypeptide. The invention also provides a polypeptide produced by this method.

Within a sixth aspect of the ivention there is provided an isolated polynucleotide encoding a fusion protein, wherein the fusion protein comprises a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer as defined above, operably linked to a second polypeptide.

Within a seventh aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a fusion protein as disclosed above; and a transcription terminator. The invention further provides a cultured cell comprising this expression vector, wherein the cell expresses the DNA segment and produces the encoded fusion protein. Also provided is a method of producing a protein comprising culturing the cell under conditions whereby the DNA segment is expressed, and recovering the second polypeptide. Within one embodiment the recovered second polypeptide is joined to a portion of a protein of SEQ ID NO: M, wherein M is an even integer as defined above.

Within a further aspect of the invention there is provided a computerreadable medium encoded with a data structure comprising SEQ ID NO:X, wherein X is an integer from 1 to 422.

Within an additional aspect of the invention there is provided an antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer as defined above.

These and other aspects of the invention will become evident upon reference to the following detailed description of the invention.

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DETAILED DESCRIPTION OF THE INVENTION

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Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms:

The term "affinity tag" is used herein to denote a polypeptide segment 5 that can be attached to a second polypeptide to provide for purification of the second polypeptide or provide sites for attachment of the second polypeptide to a substrate. In principal, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Affinity tags include a poly-histidine tract, protein A (Nilsson et al., EMBO J. 4:1075, 1985; Nilsson et al., Methods Enzymol. 10 198:3, 1991), glutathione S transferase (Smith and Johnson, Gene 67:31, 1988), Glu-Glu affinity tag (Grussenmeyer et al., Proc. Natl. Acad. Sci. USA 82:7952-7954, 1985; see SEQ ID NO:423), substance P, Flag[™] peptide (Hopp et al., Biotechnology 6:1204-1210, 1988), maltose binding protein (Kellerman and Ferenci, Methods Enzymol. 90:459-463, 1982; Guan et al., Gene 67:21-30, 1987), streptavidin binding peptide, thioredoxin, ubiquitin, cellulose binding protein, T7 polymerase, immunoglobulin constant domain, or other antigenic epitope or binding domain. See, in general, Ford et al., Protein Expression and Purification 2: 95-107, 1991. Affinity tags can be used individually or in combination. DNAs encoding affinity tags and otehr reagents are available from commercial suppliers (e.g., Pharmacia Biotech, Piscataway, NJ; Eastman Kodak, New Haven, CT; New England Biolabs, Beverly, MA).

The term "allelic variant" is used herein to denote any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and may result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequence. The term allelic variant is also used herein to denote a protein encoded by an allelic variant of a gene.

The terms "amino-terminal" and "carboxyl-terminal" are used herein to denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete polypeptide.

A "complement" of a polynucleotide molecule is a polynucleotide 35 molecule having a complementary base sequence and reverse orientation as compared to a reference sequence. For example, the sequence 5' ATGCACGGG 3' is complementary to 5' CCCGTGCAT 3'.

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"Corresponding to", when used in reference to a nucleotide or amino acid sequence, indicates the position in a second sequence that aligns with the reference position when two sequences are optimally aligned.

The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons encompass different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription, wherein said segments are arranged in a way that does not exist naturally. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

The term "isolated", when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, *Nature* 316:774-78, 1985).

An "isolated" polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide or protein is substantially free of other polypeptides or proteins, particularly other polypeptides or proteins of animal origin. It is preferred to provide the polypeptides or proteins in a highly purified form, i.e. greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same polypeptide or protein in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

A "mature protein" is a protein that is produced by cellular processing of a primary translation product of a DNA sequence. Such processing may include

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removal of a secretory signal peptide, sometimes in combination with a propeptide. Mature sequences can be predicted from full-length sequences using methods known in the art for predicting cleavage sites. See, for example, von Heijne (Nuc. Acids Res. 14:4683, 1986). The sequence of a mature protein can be determined experimentally by expressing a DNA sequence of interest in a eukaryotic host cell and determining the amino acid sequence of the final product. For proteins lacking secretory peptides, the primary translation product will be the mature protein.

"Operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator. When referring to polypeptides, "operably linked" includes both covalently (e.g., by disulfide bonding) and non-covalently (e.g., by hydrogen bonding, hydrophobic interactions, or salt-bridge interactions) linked sequences, wherein the desired function(s) of the sequences are retained.

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The term "ortholog" denotes a polypeptide or protein obtained from one species that is the functional counterpart of a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

"Paralogs" are distinct but structurally related proteins made by an organism. Paralogs are believed to arise through gene duplication. For example, α -globin, β -globin, and myoglobin are paralogs of each other.

A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired. Such unpaired ends will in general not exceed 20 nt in length.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10 amino acid residues are commonly referred to as "peptides".

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The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

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A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

A "secretory signal sequence" is a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

The present invention is based in part upon the discovery of a group of novel, protein-enoding DNA molecules. These DNA molecules and the amino acid sequences that they encode are shown in SEQ ID NO:1 through SEQ ID NO:436. Sequence analysis predicts that each of the encoded proteins includes an aminoterminal secretory peptide. These secretory peptides are shown below in Table 1, wherein residue numbers are in reference to the indicated SEQ ID NO. As will be understood by those skilled in the art, the cleavage sites predicted by conventional models of secretory peptide cleavage (e.g., von Heijne, *Nuc. Acids Res.* 14:4683, 1986) are not always exact and may vary by as much as ± 5 residues. In addition, cleavage may occur at multiple sites within 5 residues of the indicated position. The mature form of any given protein may thus consists of a plurality of species differing at their amino termini.

Table 1

<u>Protein</u>	SEQ ID NO:	Residues 1-
AFP210015	2	14
AFP170681	4	26
AFP413680	6	28
AFP483037	8	14
AFP230872	10	27
AFP178828	12	14
AFP200134	14	23
AFP195796	16	22
AFP477303	18	18
AFP354334	20	25
AFP250287	22	17
AFP177000	24	26
AFP278176	26	21
AFP202885	28	18
AFP221312	30	23
AFP239757	32	22
AFP226311	34	20
AFP305901	36	20
AFP325549	38	20
AFP81988	40	14
AFP199200	42	20
AFP290395	44	23
AFP212675	46	20
AFP326051	48	17
AFP512441	50	18
AFP55098	52	15
AFP169796	54	21
AFP280706	56	25
AFP383165	58	23
AFP195467	60	26
AFP134225	62	22
AFP261193	64	28
AFP324422	66	28
AFP374312	68	28
AFP258118	70	24
AFP74517	72	25
AFP254653	74	18
AFP108666	76	21
AFP8766	78	15
AFP397185	80	20
AFP195042	82	21
AFP310695	84	
AFP70022	86	26
AFP121670		19 22
AFP345861	88	22
AFF343801	90	15

AFP395942	92	16
AFP170291	94	21
AFP297548	96	22
AFP188135	98	28
AFP302388	100	19
AFP263430	102	17
AFP201273	104	18
AFP98983	106	25
AFP581958	108	20
AFP404202	110	19
AFP207203	112	15
AFP220790	114	19
AFP536326	116	23
AFP257473	118	22
AFP248380	120	16
AFP276202	122	20
AFP227568	124	23
AFP229039	126	20
AFP176297	128	17
AFP356885	130	17
AFP226938	132	16
AFP138504	134	29
AFP359196	136	24
AFP501809	138	27
AFP152733	140	15
AFP541394	142	23
AFP243183	144	20
AFP80739	146	18
AFP361806	148	26
AFP483930	150	21
AFP257336	152	25
AFP195800	154	23
AFP179530	156	19
AFP279267	158	14
AFP299766	160	29
AFP244615	162	16
AFP325761	164	22
AFP226024	166	22
AFP257094	168	27
AFP197103	170	27
AFP271855	172	17
AFP324816	174	29
AFP407963	176	25
AFP369635	178	17
AFP93743	180	28
AFP243230	182	15
AFP169316	184	21
AFP130852	186	15
	100	13

AFP194191	188	22
AFP213472	190	21
AFP360430	192	22
AFP491309	194	21
AFP193428	196	23
AFP366534	198	22
AFP22706	200	27
AFP389012	202	14
AFP137186	204	24
AFP127023	206	21
AFP389687	208	16
AFP293220	210	25
AFP425535	212	25
AFP301494	214	25
AFP345421	216	19
AFP216667	218	26
AFP247951	220	29
AFP4464	222	22
AFP561930	224	28
AFP192851	226	22
AFP252759	228	20
AFP199044	230	20
AFP357958	232	28
AFP117501	234	15
AFP194554	236	23
AFP371069	238	23
AFP313600	240	19
AFP262739	242	18
AFP180730	244	27
AFP287227	246	28
AFP75785	248	26
AFP174843	250	15
AFP250422	252	15
AFP198645	254	17
AFP238111	256	16
AFP460626	258	24
AFP271081	260	14
AFP277752 AFP291338	262	16
AFP551038	264	15
AFP301579	266	22
AFP266188	268	20
AFP275580	270 272	16
	272	28
AFP298054 AFP348226	274	21
-	276	23
AFP349106	278	23
AFP288248	280	15
AFP436476	282	19

AFP352125	284	14
AFP62060	286	25
AFP236718	288	21
AFP75775	290	25
AFP407487	292	23
AFP280451	294	27
AFP11675	296	29
AFP348656	298	16
AFP277451	300	19
AFP287436	302	14
AFP116043	304	28
AFP138740	306	26
AFP15192	308	17
AFP169968	310	27
AFP173341	312	23
AFP17588	314	23
AFP176427	316	20
AFP192633	318	14
AFP193013	320	15
AFP193881	322	16
AFP195562	324	16
AFP199922	326	18
AFP204736	328	17
AFP206179	330	27
AFP221877	332	23
AFP222758	334	26
AFP227032	336	24
AFP229269	338	27
AFP232213	340	25
AFP237679	342	21
AFP249599	344	28
AFP275215	346	21
AFP290397	348	26
AFP306591	350	18
AFP310297	352	20
AFP314720	354	19
AFP318671	356	29
AFP323575	358	21
AFP327160	360	20
AFP329002	362	29
AFP345415	364	24
AFP347179	366	24
AFP359138	368	23
AFP365372	370	17
AFP367284	372	23
AFP372822	374	26
AFP374595	376	29
AFP375952	378	25

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AFP382913	380	17
AFP389184	382	23
AFP404208	384	20
AFP404279	386	29
AFP409112	388	26
AFP413111	390	19
AFP415635	392	15
AFP421092	394	17
AFP436666	396	25
AFP448623	398	19
AFP454192	400	20
AFP49026	402	28
AFP51688	404	28
AFP525341	406	16
AFP545268	408	15
AFP592620	410	22
AFP62197	412	23
AFP68229	414	25
AFP71288	416	15
AFP77851	418	27
AFP81957	420	15
AFP85168	422	27

A secretory peptide of a protein of the present invention can be used to direct the secretion of other proteins of interest from a host cell. Thus, the present invention provides, inter alia, fusions comprising such a secretory peptide of a protein disclosed herein operably linked to another protein of interest. The secretory peptide can be used to direct the secretion of other proteins of interest by joining a polynucleotide sequence encoding it, in the correct reading frame, to the 5' end of a sequence encoding the other protein of interest. Those skilled in the art will recognize that the resulting fused sequence may encode additional residues of a protein of the present invention at the amino terminus of the protein to be secreted. In the extreme case, the fusion may comprise an entire protein of the present invention fused to the amino terminus of a second protein, whereby secretion of the fusion protein is directed by the secretory peptide of the protein of the present invention. It will often be desirable to include a proteolytic cleavage site between the protein of the present 15 invention (or portion thereof) and the other protein of interest. polynucleotide sequences are then introduced into a host cell, which is cultured according to conventional methods. The protein of interest is then recovered from the culture media. Methods for introducing DNA into host cells, culturing the cells, and isolating recombinant proteins are known in the art. Representative methods are summarized below.

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Within certain embodiments of the invention, the protein is selected from those listed in Table 2. Within related embodiments of the invention, the polynucleotide is selected from polynucleotides encoding the proteins listed in Table 2, i.e., for a protein of SEQ ID NO:M, the polynucleotide is SEQ ID NO:M-1.

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Table 2

SEQ ID NO:	Protein	SEQ ID NO:	Protein
6	AFP413680	234	AFP117501
12	AFP178828	. 236	AFP194554
18	AFP477303	240	AFP313600
24	AFP177000	242	AFP262739
42	AFP199200	252	AFP250422
48	AFP326051	254	AFP198645
66	AFP324422	258	AFP460626
68	AFP374312	270	AFP266188
72	AFP74517	272	AFP275580
90	AFP345861	288	AFP236718
92	AFP395942	294	AFP280451
96	AFP297548	300	AFP277451
98	AFP188135	306	AFP138740
110	AFP404202	324	AFP195562
134	AFP138504	338	AFP229269
138	AFP501809	342	AFP237679
156	AFP179530	344	AFP249599
158	AFP279267	348	AFP290397
162	AFP244615	350	AFP306591
164	AFP325761	366	AFP347179
174	AFP324816	374	AFP372822
180	AFP93743	378	AFP375952
204	AFP137186	386	AFP404279
206	AFP127023	396	AFP436666
210	AFP293220	398	AFP448623
224	AFP561930	408	AFP545268
230	AFP199044	416	AFP71288

Higher order structures of the proteins of the present invention can be predicted by computer analysis using available software (e.g., the Insight II® viewer and homology modeling tools available from MSI, San Diego, CA; and King and Sternberg, *Protein Sci.* 5:2298-310, 1996). In addition, analytical algorithms permit the identification of homologies between newly discovered proteins and known proteins. Such homologies are indicative of related biological functions.

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AFP254653 is 49% identical in sequence to human lysozyme C. Lysozyme C is a secreted bacteriolytic enzyme with similarity to the alphalactalbumins. Both are small alpha + beta proteins with six conserved cysteines forming a disulfide core comprising three disulfide bonds. AFP254653 may also exhibit bacteriolytic or other antimicrobial activity.

AFP581958 is 43% identical to wheat aluminum-induced protein, a member of the Bowman-Birk proteinase inhibitor family. All serine proteinases possess an exposed inhibitor loop that is stabilized by intermolecular interactions (usually disulfide bonds) between residues flanking the binding loop and the protein core. Interaction between inhibitor and enzyme produces a stable complex that disassociates very slowly, producing either an unaffected or a modified inhibitor that is cleaved at the scissile bond of the binding loop. AFP581958 may be a secreted serine proteinase.

AFP220790 is 42% identical to chicken lysozyme G, a bacteriolytic glycosyl hydrolase that hydrolizes peptidoglycan homopolymers of the prokaryote cell walls. AFP220790 may thus be a secreted bacteriolytic enzyme, and may exhibit other antimicrobial activity.

AFP271855 is 37% identical to bovine granulocyte peptide A precursor (antimicrobial BGP-A). Bovine and murine granulocyte peptide A precursor (also called antimicrobial BGP-A) are disclosed in WIPO publication WO 97/29765. Bovine GP-A was isolated from a bone marrow library (WO 97/29765). GP-A exhibits activity against Gram-positive and Gram-negative bacteria, fungi and viruses. AFP271855 may exhibit antimicrobial (including one or more of anti-bacterial, anti-fungal, and antiviral) activity.

AFP298054 is 24% identical to human T1/ST2 ligand. The T1 gene is also known as ST2, DER4, and Fit-1. It encodes a member of the interleukin-1 (IL-1) receptor family. It is transcribed in two forms, a soluble form and a membrane-bound form. The classical IL-1 ligands (IL-1α, IL-1β, and IL-1ra) do not bind T1. A putative ligand for T1 was disclosed in 1996 (Gayle et al., *J. Biol. Chem.* 227:5784-5789, 1996).

This protein binds T1 but is unable to initiate signal transduction by the membrane-bound form. The ligand is apparently a type I membrane protein. It has a predicted molecular weight (excluding the signal sequence and transmembrane domain) of about 22 kD, and has no sequence or hydrophobicity profile similarity to the beta-trefoil cytokines IL-1 or the FGFs. AFP298054 may be an antagonist that binds the receptor and regulates the activity of an as yet undiscovered IL-1 homolog.

Table 3 lists homologies between AFP sequences and sequences contained in the GenBank database, Derwent protein (PSP) or polynucleotide (PSN) databases, or Protein Identification Resource (PIR).

5 Table 3

	1 able 3
Locus	Accession Number & Description
AFP130852	AE003823 (fly genomic)
AFP169968	AE003515 (fly genomic)
AFP174843	AF283518 (Mus musculus elongation factor sec)
AFP176427	AE003808 (fly genomic)
AFP178828	PSN_V61483
AFP179530	AE003708 (fly genomic)
AFP188135	AE003677 (fly genomic)
AFP195042	PIR_T41241 (yeast oxysterol-binding protein family)
AFP198645	AE003718 (fly genomic)
AFP199200	AF113691 (human clone FLB4739 PRO1238 mRNA)
AFP204736	AC069237 (human chromosome 3 clone RP11-175M9)
AFP229269	AF247177 (Mus musculus sphingosine-1-phosphate
	phosphohydrolase)
AFP230872	AF150741 (Rattus norvegicus prolactin-like protein J mRNA)
AFP279267	AE003559 (fly genomic)
AFP347179	AE003499 (fly genomic) Z1041035F6P
AFP357958	AF283518 (Mus musculus elongation factor sec mRNA)
AFP359196	AE003530 (fly genomic)
AFP374312	AE003538 (fly genomic)
AFP389687	AE003831 (fly genomic)
AFP395942	AB041564 (mouse brain cDNA; clone MNCb-0914)
AFP404202	AL137255 (human mRNA; cDNA DKFZp434B1813)
AFP413680	X14971 (mouse mRNA for alpha-adaptin, MMADAPA1)
AFP477303	AE003778 (fly genomic)
AFP62060	PSP_Y94938 (Human secreted protein clone ye78_1)
AFP71288	AL161655 (human chromosome 20 clone RP11-116E13)
AFP74517	PIR_T16263 (C. elegans hypothetical protein F35D11.3)

Table 4 lists AFP proteins for which regions of identity have been found in the GenBank database.

Table 4

	14010
Locus	Accession Number & Description
AFP127023	SK000740 (human cDNA FLJ20733; clone HEP08550; by homology: molybdopterin cofactor sulfurase)
AFP134225	AB020970 (human mRNA; partial cds and 3'UTR; up-regulated by BCG-CWS)
AFP195562	AK000382 (human cDNA FLJ20375; clone HUV00942)

AFP199044	HSU80813 (human nucleoside diphosphate kinase homolog DR-nm23)
AFP227032	AK001848 (human cDNA FLJ10986; clone PLACE1001869; weakly
	similar to L-RIBULOKINASE; EC 2.7.1.16)
AFP237679	AB000465 (human mRNA; exon 1; 2; 3; 4; clone:RES4-24B; in
	genomic region of Huntington's disease locus)
AFP262739	AK000135 (human cDNA FLJ20128; clone COL06181)
AFP369635	PSN_Z24827 (Human secreted protein gene 17 clone HNFIY77)
AFP81957	AF267730 (human 26S proteasome-associated UCH interacting protein
	1; UIP1)
AFP93743	AK000066 (human cDNA FLJ20059; clone COL01349)

Table 5 lists AFP proteins for which longer regions of identity have been found in proteins contained in GenBank and other databases.

Table 5

1 able 5		
Locus	Accession Number & Description	
AFP117501	AK000505 (human cDNA FLJ20498; clone KAT08960)	
AFP138740	HSM802370 (human mRNA; cDNA DKFZp434M1511)	
AFP170291	AK000494 (human cDNA FLJ20487; clone KAT08245)	
AFP170681	AK001698 (human cDNA FLJ10836; clone NT2RP4001228 close	
	paralogue of human Kelch-like 1 protein (KLHL1) mRNA: AF252283)	
AFP177000	AK000524 (human cDNA FLJ20517; clone KAT10235)	
AFP193881	AK000382 (human cDNA FLJ20375; clone HUV00942)	
AFP195796	AF251041 (human SGC32445 protein (SGC32445) mRNA; homology	
	to PSP_W35393 Human TB2 gene product)	
AFP202885	AB037808 (human mRNA for KIAA1387 protein)	
AFP207203	AF250924 (human PNGase mRNA: peptide N-glycanase)	
AFP226024	AK001952 (human cDNA FLJ11090; clone PLACE1005308)	
AFP227568	AB019038 (human HMT-1 mRNA for beta-1;4 mannosyltransferase)	
AFP244615	AK001009 (human cDNA FLJ10147; clone HEMBA1003369; weak	
	homology: CENE_HUMAN CENTROMERIC PROTEIN E)	
AFP250422	AF208849 (human BM-007 mRNA)	
AFP266188	AK000272 (human cDNA FLJ20265; clone COLF9334; homology to	
	major facilitator protein homolog, fission yeast: PIR_S62432)	
AFP277451	AK001373 (human cDNA FLJ10511; clone NT2RP2000656)	
AFP277752	AK000453 (human cDNA FLJ20446; clone KAT05231; weak	
	homology to dinitrogenase reductase activating glycohydrolase (draG)	
	Archaeoglobus fulgidus: PIR_C69465)	
AFP280451	AL133355 (Human DNA sequence from clone RP11-541N10 on	
	chromosome 10. Contains a novel gene and the 5' end of the gene for a	
	novel protein; ortholog of mouse FISH protein)	
AFP293220	AK001441 (human cDNA FLJ10579; clone NT2RP2003446)	
AFP297548	AK000494 (human cDNA FLJ20487; clone KAT08245)	
AFP306591	AL359700 (human chromosome 6 clone RP11-802L12)	
AFP324816	AB032966 (human mRNA for KIAA1140 protein weak homology:	
	Human O-linked GlcNAc transferase mRNA)	

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AFP356885	AK001544 (human cDNA FLJ10682; clone NT2RP3000072)
AFP389012	AK000428 (human cDNA FLJ20421; clone KAT02467; homologus to
	human bisphosphate 3'-nucleotidase mRNA: AF125042)
AFP436666	AK001608 (human cDNA FLJ10746; clone NT2RP3001679; likely
	human orthologue of Rattus norvegicus small rec (srec) mRNA:
	AF228917)
AFP501809	AK001963 (human cDNA FLJ11101; clone PLACE1005623)
AFP525341	AF189692 (human non-kinase Cdc42 effector protein SPEC2 mRNA)

A protein of the present invention can be prepared as a fusion protein by joining it to a second polypeptide or a plurality of additional polypeptides. Suitable second polypeptides include amino- or carboxyl-terminal extensions, such as linker peptides of up to about 20-25 residues and extensions that facilitate purification (affinity tags) as disclosed above. A protein of interest can be prepared as a fusion to a dimerizing protein as disclosed in U.S. Patents Nos. 5,155,027 and 5,567,584. Preferred dimerizing proteins in this regard include immunoglobulin constant region domains. Immunoglobulin-polypeptide fusions can be expressed in genetically 10 engineered cells to produce a variety of multimeric analogs of a protein of interest. Fusion proteins can also comprise auxiliary domains that target the protein of interest to specific cells, tissues, or macromolecules (e.g., collagen). For example, a protein of interest can be targeted to a predetermined cell type by fusing it to a ligand that specifically binds to a receptor on the surface of a target cell. In this way, proteins can be targeted for therapeutic or diagnostic purposes. A protein can be fused to two or more moieties, such as an affinity tag for purification and a targeting domain. Protein fusions can also comprise one or more cleavage sites, particularly between domains. See, Tuan et al., Connective Tissue Research 34:1-9, 1996. Proteins of the present invention can also be used as targetting moieties within fusion proteins comprising, for example, cytokines, cytotoxins, or other biologically active polypeptide moieties.

Protein fusions of the present invention will usually contain not more than about 1,200 amino acid residues joined to the AFP protein. For example, an AFP protein can be fused to *E. coli* β -galactosidase (1,021 residues; see Casadaban et al., *J. Bacteriol.* 143:971-980, 1980), a 10-residue spacer, and a 4-residue factor Xa cleavage site. Such a protein comprising, for example, AFP345421 (SEQ ID NO:216), contains 2235 amino acid residues. In a second example, an AFP protein can be fused to maltose binding protein (approximately 370 residues), a 4-residue cleavage site, and a 6-residue polyhistidine tag.

As disclosed above, the proteins of the present invention or portions thereof can also be used to direct the secretion of a second protein. When such fusions

are designed so that the secreted protein retains a portion of the protein of the present invention, the fusion protein can be purified by means that exploit the properties of the protein of the present invention. Typical of such methods is immunoaffinity chromatography using an antibody directed against a protein of the present invention. When such a fusion is engineered to contain a cleavage site at the fusion point, the fusion can be cleaved and the protein of interest recovered free of extraneous sequence.

The present invention also provides polynucleotide molecules, including DNA and RNA molecules, that encode the proteins disclosed above. Those skilled in the art will readily recognize that, in view of the degeneracy of the genetic code, considerable sequence variation is possible among these polynucleotide molecules. The amino acid sequence information provided herein can be used by one of ordinary skill in the art to generate degenerate sequences comprising all nucleotide sequences encoding a particular polypeptide. Table 6 sets forth the one-letter codes used to denote degenerate nucleotide positions. "Resolutions" are the nucleotides denoted by a code letter. "Complement" indicates the code for the complementary nucleotide(s). For example, the code Y denotes either C or T, and its complement R denotes A or G, A being complementary to T, and G being complementary to C.

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TABLE 6

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	Nucleotide	Resolutions	Complement	Resolutions
-	Α	Α ,	T	T
	С	C	G	G
	G	G	C	С
	T	Т	Α	Α
	R	A G	Y	C T
	Y	С T	R	A G
	M	A C	K	G T
	K	G T	M	A C
	S	C G	S	C G
	W	A T	W	A T
	Н	A C T	D	A G T
	В	C G T	v	A C G
	V	A C G	В	C G T
	D	AIGIT	Н	A C T
	N	A C G T	N	A C G T

Degenerate codons encompassing all possible codons for a given amino acid are set forth in Table 7, below.

TABLE 7

Amino One-Letter Degenerate Acid Code Codons Codon Cys C TGC TGT TGY Ser S AGC AGT TCA TCC TCG TCT WSN Thr T ACA ACC ACG ACT CAN Pro P CCA CCC CCG CCT CCN Ala A GCA GCC GCG GCT GCN Gly G GGA GGC GGG GGT GGN Asn N AAC AAT AAY Asp D GAC GAT GAY Glu E GAA GAG GAR Gln Q CAA CAG CAR His H CAC CAT CAY Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ATH	
Ser S AGC AGT TCA TCC TCG TCT WSN Thr T ACA ACC ACG ACT CAN Pro P CCA CCC CCG CCT CCN Ala A GCA GCC GCG GCT GCN Gly G GGA GGC GGG GGT GGN Asn N AAC AAT AAY Asp D GAC GAT GAY Glu E GAA GAG GAR Gln Q CAA CAG CAR His H CAC CAT CAY Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ACC ACT ATG	
Thr T ACA ACC ACG ACT CAN Pro P CCA CCC CCG CCT CCN Ala A GCA GCC GCG GCT GCN Gly G GGA GGC GGG GGT GGN Asn N AAC AAT AAY Asp D GAC GAT GAY Glu E GAA GAG GAR Gln Q CAA CAG CAR His H CAC CAT CAY Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ATG	
Pro P CCA CCC CCG CCT CCN Ala A GCA GCC GCG GCT GCN Gly G GGA GGC GGG GGT GGN Asn N AAC AAT AAY Asp D GAC GAT GAY Glu E GAA GAG GAR Gln Q CAA CAG CAR His H CAC CAT CAY Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ACC	
Ala A GCA GCC GCG GCT GCN Gly G GGA GGC GGG GGT GGN Asn N AAC AAT AAY Asp D GAC GAT GAY Glu E GAA GAG GAR Gln Q CAA CAG CAR His H CAC CAT CAY Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ATG	
Gly G GGA GGC GGG GGT GGN Asn N AAC AAT AAY Asp D GAC GAT GAY Glu E GAA GAG GAR Gln Q CAA CAG CAR His H CAC CAT CAY Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ATG	
Asn N AAC AAT AAY Asp D GAC GAT GAY Glu E GAA GAG GAR Gln Q CAA CAG CAR His H CAC CAT CAY Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ATG	
Asp D GAC GAT GAY Glu E GAA GAG GAR Gln Q CAA CAG CAR His H CAC CAT CAY Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ATG	
Glu E GAA GAG GAR Gln Q CAA CAG CAR His H CAC CAT CAY Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ATG	
Gln Q CAA CAG CAR His H CAC CAT CAY Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ATG	
His H CAC CAT CAY Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ATG	
Arg R AGA AGG CGA CGC CGG CGT MGN Lys K AAA AAG AAR Met M ATG ATG	
Lys K AAA AAG AAR Met M ATG ATG	
Met M ATG ATG	
Ile I ATA ATC ATT ATH	

Leu L CTA CTC CTG CTT TTA TTG YTN	
Val V GTA GTC GTG GTT GTN	
Phe F TTC TTT TTY	
Tyr Y TAC TAT TAY	
Trp W TGG TGG	
Ter . TAA TAG TGA TRR	
Asn Asp B RAY	
Glu Gln Z SAR	
Any X NNN	
Gap	

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One of ordinary skill in the art will appreciate that some ambiguity is introduced in determining a degenerate codon, representative of all possible codons encoding each amino acid. For example, the degenerate codon for serine (WSN) can, in some circumstances, encode arginine (AGR), and the degenerate codon for arginine (MGN) can, in some circumstances, encode serine (AGY). A similar relationship

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exists between codons encoding phenylalanine and leucine. Thus, some polynucleotides encompassed by the degenerate sequences may encode variant amino acid sequences, but one of ordinary skill in the art can easily identify such variant sequences by reference to the amino acid sequences disclosed in the accompanying Sequence Listing.

Methods for preparing DNA and RNA are well known in the art. Complementary DNA (cDNA) clones are prepared from RNA that is isolated from a tissue or cell that produces large amounts of the cognate mRNA. Such tissues and cells are identified by methods commonly known in the art, such as Northern blotting 10 (Thomas, Proc. Natl. Acad. Sci. USA 77:5201, 1980). Databases of expressed sequence tags (ESTs) can be analyzed to produce an "electronic Northern" wherein sequences are assigned to specific cell or tissue sources on the basis of their abundance within libraries. Table 8, below, shows the results of such an analysis when, as the minimum significant abundance, it was required that at least 10% of all sequences for a given protein were from a single source and at least five individual clones had been identified from that source. Sequences shown in the accompanying Sequence Listing but not listed in Table 8 were widely distributed among various tissues or were represented by few clones.

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Table 8

AFP152733	K562 cells
AFP169796	T-cells
AFP173341	testis
AFP17588	fetal liver or spleen
AFP194554	fetal liver or spleen
AFP199922	testis
AFP229269	placenta
AFP237679	fetal liver or spleen
AFP257094	adult brain
AFP258118	epidermal breast keratinocytes
AFP263430	breast
AFP276202	infant brain
AFP287436	testis
AFP290397	testis
AFP306591	fetal heart
AFP325761	K562 cells
AFP352125	testis
AFP359138	infant brain
AFP369635	germinal center B-cells
AFP409112	kidney
AFP483037	neonatal keratinocytes
AFP49026	peripheral blood eosinophils of asthma patients
AFP545268	K562 cells
AFP561930	fetal liver or spleen
AFP62060	testis
AFP62197	pregnant uterus
AFP93743	germinal center B-cells
AFP98983	fetal heart

A panel of cDNAs from human tissues was screened for AFP expression using PCR. The panel was made from first strand cDNAs obtained from Clontech laboratories, Inc., Palo Alto, CA and contained 20 first-strand cDNA samples from the human tissues shown in Table 9. The panel was set up in a 96-well format that further included a human genomic DNA (obtained from Clontech Laboratories, Inc.) positive control sample and a water-only well as a negative control sample. Each well contained approximately 0.2-100 pg/µl of cDNA, diluted with water to 17.5µl. The

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PCR reactions were set up by adding oligonucleotide primers, DNA polymerase (Ex TaqTM; TAKARA Shuzo Co. Ltd. Biomedicals Group, Japan or AdvantageTM 2 cDNA polymerase mix; Clontech Laboratories, Inc.) with the appropriate supplied buffer, dNTP mix (TAKARA Shuzo Co. Ltd.), and a density increasing agent and tracking dye (RediLoad; Research Genetics, Inc., Huntsville, AL) to each sample on the panel. The amplification was carried out as follows: incubation at 94°C for 2 minutes; 35 cycles of 94°C for 30 seconds, 60°C for 20 seconds, and 72°C for 30 seconds; followed by incubation at 72°C for 5 minutes. About 10 μl of the PCR reaction product was subjected to standard agarose gel electrophoresis using a 4% agarose gel.

	г	Т	Т	Т	Т	_	T	Т	_	Т	Т	т-	Т	Т	Т	1	Т	Т	Т	Т	Τ-	Т	Τ-	т-	_	_	Т	1	_	T	т-	_	
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	13	^	^	_	<u>_</u>	\ <u>_</u>	>	\ -	>	>	^	_	=	_	^	=	=	γ	λ	_	γ	y	λ	у	λ		_	'n	У	_	_	^	_
Table 9	12	^	_	_	>	_>	>	_	>	-	_	_	c	_	^	y	_	y	У	۵	y	У	у.	У	у	^	^	^	y	×	y	y	E .
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-	2	У	Υ	Y	y	y	у	У	λ	У	ý	^	c	u	^	^	Y	λ	_	ء	2	>	2	^	2	2	_	7	>	>	>	>	_
	4	^	^	^	^	^	y	у	Ý	,	^		_	'n	츼	^	'n	^	7	=	ᅿ	ᅿ	ᅿ	7	^	7	4	^	7	7	7	>	=
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	1	=	23	9	정	ဒ္ဓ	ျှ	82	စ္က	35	7	2	స్		\dashv	\dashv	┪	7	2	7	7	+	+	္က	_	5	_	7		7	\dashv	+	٦
	Protein	AFP117501	AFP127023	AFP137186	AFP138504	AFP138740	AFP177000	AFP178828	AFP179530	AFP188135	AFP194554	AFP195562	AFP198645	AFP199044	AFP199200	AFP229269	AFP236718	AFP237679	AFP244615	AFP249599	AFP250422	AFP262739	AFP266188	AFP275580	AFP277451	AFP279267	AFP280451	AFP290397	AFP293220	AFP297548	AFP30659	AFP313600	AFP324422

Table 9, continued	tinued																					
Protein	1	2	3	4	5	9	1	8	6	01	=	12	13	4	15	91	12	81	6	20	21	22
AFP324816	y	y	y	y	y.	y	_	_	^	^	^	×	Y	_	^	^	^	>	>	_	_	>
AFP325761	y	y	y	y	γ	y	_	_	_	^	_	_	ء	_	_	_	_	_	_	_	=	_=
AFP326051	у	y	y	y	×	^	_			_	_	λ,	ý	^	_		>	_	_	_	_	>
AFP345861	y	y	y	у	y	y	一	밀	밀	_	밀	^	pu	ē	_	_	>	_>	>	_	_	
AFP347179	У	y	l y	у	y	y	^	\	_	_	^	_	=	^	,	_	-	_	\	-	_	>
AFP372822	У	у	y	ý	γ	_	_	ļ	_	_	>	ν,	y	_	, ,	_	>	_	_	>	_	_
AFP374312	c	_	y	y	ū	u	u	u	u	=	_	_	_	_	_	_	^	^	_		_	_
AFP375952	u	п	u	u	u	u	r.	ے	_	_	_	_	_	_	_	_	=	_	_	_	_	>
AFP395942	γ	'n	y	y	y	y	Ž	^	ے	_	_	y	=	^	ء	_	_>	_	_	>	_	>
AFP404202	λ	Λ	y	y	y	y) }	u	\ \	×	_	^	_	_	^	`^	^	, ,	_	,	_	_
AFP404279	አ	y	y	У	u	y	у.	u	_	_	_	^	^	_	^	^	٦	_	_	_	_	_
AFP413680	λ	^	y	у	y	y	y	y	у	y	y	У	^	^	^	_	2		_		_	_
AFP436666	^	^	2	ý	y	y	y	y	u	y	y .	y	u	У	y	_	^	_	_	_	_	_
AFP448623	'n	c	^	u	п	y	u	u	u	_	u	=	u	u	^	_	_	^	^	_	_	_
AFP460626	^	>	λ	y	y	y	y	y	y	y	y	y	у	y	٧	Ý	밀	_	^	_	_	_
AFP477303	^	^	Ż	у	y	y	y	y	У	y	y	y	7	>	_	^	^	_	_	_	_	_
AFP501809	^	V	λ	y.	y	у	y	y) }	^	>	· .	>	>	_	_	~	_	\	^	_	_
AFP545268	у	y	У	y	y	y.	y	y	y	y	^	>	^	^	^	^	>	^	^	,	_	>
AFP561930	λ	>	>	Ž	y	y	y	pu	y	y	u	y	у	pu	y	y	\ \ \	_	뎔	_	_	
AFP71288	c	E	L	u	n	u	u	c	u	u	u	u	u	u	u	٦	=	ے	=	_	=	_
AFP74517	^	_	Ż	Ż	χ	y	y	y	y	у	y	у	у	У	У	y	λ	^	_	^	_	_
AFP93743	ý	y	^	Ż	У	y	, _	y	У .	^	<u>۸</u>	y	y	y	y	У	y	y	y	γ	u	>

Tissues screened were: 1, brain; 2, heart; 3, kidney; 4, liver; 5, lung; 6, pancreas; 7, placenta; 8, skeletal muscle; 9, colon; 10, ovary; 11, peripheral blood leukocytes; 12, prostate; 13, small intestine; 14, spleen; 15, testis; 16, thymus; 17, bone marrow; 18, fetal liver; 19, lymph node; 20, tonsil; 21, H₂O; 22, genomic DNA. Y=yes; n=no; nd=not determined.

Total RNA can be prepared using guanidine HCl extraction followed by isolation by centrifugation in a CsCl gradient (Chirgwin et al., *Biochemistry* 18:52-94, 1979). Poly (A)+ RNA is prepared from total RNA using the method of Aviv and Leder (*Proc. Natl. Acad. Sci. USA* 69:1408-1412, 1972). Complementary DNA (cDNA) is prepared from poly(A)+ RNA using known methods. In the alternative, genomic DNA can be isolated. For some applications (e.g., expression in transgenic animals) it may be preferable to use a genomic clone, or to modify a cDNA clone to include at least one genomic intron. Methods for identifying and isolating cDNA and genomic clones are well known and within the level of ordinary skill in the art, and include the use of the sequences disclosed herein, sequences complementary thereto, or parts thereof, for probing or priming a library. Such methods include, for example, hybridization or polymerase chain reaction ("PCR", Mullis, U.S. Patent 4,683,202). Expression libraries can be probed with antibodies to a protein of interest, receptor fragments, or other specific binding partners.

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The polynucleotides of the present invention can also be prepared by automated synthesis. Synthesis of polynucleotides is within the level of ordinary skill in the art, and suitable equipment and reagents are available from commercial suppliers. See, in general, Glick and Pasternak, Molecular Biotechnology, Principles & Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994; Itakura et al., Ann. Rev. Biochem. 53: 323-56, 1984; and Climie et al., Proc. Natl. Acad. Sci. USA 87:633-7, 1990.

The present invention further provides antisense polynucleotides that are complementary to a segment of a polynucleotide as set forth in one of SEQ ID NO:N, wherein N is an odd integer from 1 to 435. Such antisense polynucleotides are designed to bind to the corresponding mRNA and inhibit its translation. Antisense polynucleotides are used to inhibit gene expression in cell culture or in a patient, and can be used as probes or primers for research or diagnostic purposes.

Probes and primers of the present invention comprise a suitable fragment, and may comprise up to the complete sequence, of a polynucleotide as shown in SEQ ID NO:N or the complement thereof, wherein N is an odd integer from 1 to 421. Probes will generally be at least 20 nucleotides in length, although somewhat shorter probes (14-17 nucleotides) can be used. PCR primers are at least 5 nucleotides in length, preferably 15 or more nt, more preferably 20-30 nt. Shorter polynucleotide probes and primers are referred to in the art as "oligonucleotides," and can be DNA or RNA. Probes will generally comprise an oligonucleotide linked to a label, such as a radionuclide.

Probes and primers as disclosed herein can be used for cloning allelic, orthologous, and paralogous sequences. Allelic variants of the disclosed sequences can be cloned by probing cDNA or genomic libraries from different individuals according to standard procedures. Orthologous sequences can be cloned using information and compositions provided by the present invention in combination with conventional cloning techniques. For example, a cDNA can be cloned using mRNA obtained from a tissue or cell type that expresses the protein. Suitable sources of mRNA can be identified by probing Northern blots with probes designed from the sequences disclosed herein. A library is then prepared from mRNA of a positive tissue or cell line. A cDNA can then be isolated by a variety of methods, such as by probing with a complete or partial human cDNA or with one or more sets of degenerate probes based on the disclosed sequences. A cDNA can also be cloned by PCR using primers designed from the sequences disclosed herein. Within an additional method, the cDNA library can be used to transform or transfect host cells, and expression of the cDNA of interest can be detected with an antibody to the encoded protein. Similar techniques can also be applied to the isolation of genomic clones. Orthologous and paralogous sequences can be identified from libraries by probing blots at low stringency and washing the blots at successively higher stringency until background is suitably reduced.

Probes and primers disclosed herein can be used to clone 5' non-coding regions of a corresponding gene. In view of the tissue-specific expression observed for certain proteins of the invention (Tables 8 and 9), promoters of these genes are expected to provide tissue-specific expression. Such promoter elements can thus be used to direct the tissue-specific expression of heterologous genes in, for example, transgenic animals or patients treated with gene therapy. Cloning of 5' flanking sequences also facilitates production of a protein of interest by "gene activation" as disclosed in U.S. Patent No. 5,641,670. Briefly, expression of an endogenous gene in a cell is altered by introducing into its locus a DNA construct comprising at least a targeting sequence, a regulatory sequence, an exon, and an unpaired splice donor site. The targeting sequence is a 5' non-coding sequence that permits homologous recombination of the construct with the endogenous locus, whereby the sequences within the construct become operably linked with the endogenous coding sequence. In this way, an endogenous promoter can be replaced or supplemented with other regulatory sequences to provide enhanced, tissue-specific, or otherwise regulated expression.

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The polynucleotides of the present invention further include polynucleotides encoding the fusion proteins, including signal peptide fusions, disclosed above.

The present invention further provides a computer-readable medium encoded with a data structure that provides at least one of SEQ ID NO:1 through SEQ ID NO:436. Suitable forms of computer-readable media include magnetic media and optically-readable media. Examples of magnetic media include a hard or fixed drive, a random access memory (RAM) chip, a floppy disk, digital linear tape (DLT), a disk cache, and a ZIP® disk. Optically readable media are exemplified by compact discs (e.g., CD-read only memory (ROM), CD-rewritable (RW), and CD-recordable),digital versatile/video discs (DVD) (e.g., DVD-ROM, DVD-RAM, and DVD+RW), and carrier waves.

The polypeptides of the present invention, including full-length proteins, biologically active fragments, immunogenic fragments, and fusion proteins, can be produced in genetically engineered host cells according to conventional techniques. Suitable host cells are those cell types that can be transformed or transfected with exogenous DNA and grown in culture, and include bacteria, fungal cells, and cultured higher eukaryotic cells. Eukaryotic cells, particularly cultured cells of multicellular organisms, are generally preferred for the production of proteins having higher eukaryotic-type post-translational modifications (e.g., γ-carboxylation) and for making proteins, especially secretory proteins, for pharmaceutical use in humans. Techniques for manipulating cloned DNA molecules and introducing exogenous DNA into a variety of host cells are disclosed by Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, and Ausubel et al., eds., *Current Protocols in Molecular Biology*, Green and Wiley and Sons, NY, 1993.

In general, a DNA sequence encoding a polypeptide of interest is operably linked to other genetic elements required for its expression, generally including a transcription promoter and terminator, within an expression vector. The vector will also commonly contain one or more selectable markers and one or more origins of replication, although those skilled in the art will recognize that within certain systems selectable markers can be provided on separate vectors, and replication of the exogenous DNA can be achieved through integration into the host cell genome. Selection of promoters, terminators, selectable markers, vectors and other elements is a matter of routine design within the level of ordinary skill in the art. Many such elements are described in the literature and are available through commercial suppliers.

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To direct a polypeptide into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in the expression vector. The secretory signal sequence may be that of the protein of interest, or may be derived from another secreted protein (e.g., t-PA; see U.S. Patent No. 5,641,655) or synthesized *de novo*. The secretory signal sequence is operably linked to the DNA sequence encoding the protein of interest, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized protein into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the protein of interest, although certain secretory signal sequences may be positioned elsewhere in the DNA sequence of interest (see, e.g., Welch et al., U.S. Patent No. 5,037,743; Holland et al., U.S. Patent No. 5,143,830).

Cultured mammalian cells are suitable hosts for use within the present invention. Methods for introducing exogenous DNA into mammalian host cells include calcium phosphate-mediated transfection (Wigler et al., Cell 14:725, 1978; 15 Corsaro and Pearson, Somatic Cell Genetics 7:603, 1981: Graham and Van der Eb, Virology 52:456, 1973), electroporation (Neumann et al., EMBO J. 1:841-845, 1982), DEAE-dextran mediated transfection (Ausubel et al., ibid.), and liposome-mediated transfection (Hawley-Nelson et al., Focus 15:73, 1993; Ciccarone et al., Focus 15:80, 1993). The production of recombinant polypeptides in cultured mammalian cells is disclosed by, for example, Levinson et al., U.S. Patent No. 4,713,339; Hagen et al., U.S. Patent No. 4,784,950; Palmiter et al., U.S. Patent No. 4,579,821; and Ringold, U.S. Patent No. 4,656,134. Suitable cultured mammalian cells include the COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), 293 (ATCC No. CRL 1573; Graham et al., J. Gen. Virol. 36:59-72, 1977) and Chinese hamster ovary (e.g. CHO-K1; ATCC No. CCL 61) cell lines. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Rockville, Maryland. In general, strong transcription promoters are preferred, such as promoters from SV-40 or cytomegalovirus. See, e.g., U.S. Patent No. 4,956,288. Other suitable promoters include those from metallothionein genes (U.S. Patent Nos. 4,579,821 and 4,601,978) and the adenovirus major late promoter. Within an alternative embodiment, adenovirus vectors can be employed. See, for example, Garnier et al., Cytotechnol. 15:145-55, 1994.

Drug selection is generally used to select for cultured mammalian cells into which foreign DNA has been inserted. Such cells are commonly referred to as "transfectants". Cells that have been cultured in the presence of the selective agent and

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are able to pass the gene of interest to their progeny are referred to as "stable transfectants." An exemplary selectable marker is a gene encoding resistance to the antibiotic neomycin. Selection is carried out in the presence of a neomycin-type drug, such as G-418 or the like. Selection systems can also be used to increase the expression level of the gene of interest, a process referred to as "amplification." Amplification is carried out by culturing transfectants in the presence of a low level of the selective agent and then increasing the amount of selective agent to select for cells that produce high levels of the products of the introduced genes. An exemplary amplifiable selectable marker is dihydrofolate reductase, which confers resistance to methotrexate. Other drug resistance genes (e.g. hygromycin resistance, multi-drug resistance, puromycin acetyltransferase) can also be used.

Insect cells can be infected with recombinant baculovirus, commonly derived from *Autographa californica* nuclear polyhedrosis virus (AcNPV). See, King and Possee, <u>The Baculovirus Expression System: A Laboratory Guide</u>, London, Chapman & Hall; O'Reilly et al., <u>Baculovirus Expression Vectors: A Laboratory Manual</u>, New York, Oxford University Press., 1994; and Richardson, Ed., <u>Baculovirus Expression Protocols. Methods in Molecular Biology</u>, Humana Press, Totowa, NJ, 1995. Recombinant baculovirus can also be produced through the use of a transposon-based system described by Luckow et al. (*J. Virol.* <u>67</u>:4566-4579, 1993). This system, which utilizes transfer vectors, is commercially available in kit form (Bac-to-Bac™ kit; Life Technologies, Rockville, MD). See also, Hill-Perkins and Possee, *J. Gen. Virol.* <u>71</u>:971-976, 1990; Bonning et al., *J. Gen. Virol.* <u>75</u>:1551-1556, 1994; and Chazenbalk and Rapoport, *J. Biol. Chem.* <u>270</u>:1543-1549, 1995.

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For protein production, the recombinant virus is used to infect host cells, typically a cell line derived from the fall armyworm, *Spodoptera frugiperda* (e.g., Sf9 or Sf21 cells) or *Trichoplusia ni* (e.g., High Five™ cells; Invitrogen, Carlsbad, CA). See, in general, Glick and Pasternak, Molecular Biotechnology: Principles and Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994. See also, U.S. Patent No. 5,300,435. Serum-free media are used to grow and maintain the cells. Suitable media formulations are known in the art and can be obtained from commercial suppliers. The cells are grown up from an inoculation density of approximately 2-5 x 10⁵ cells to a density of 1-2 x 10⁶ cells, at which time a recombinant viral stock is added at a multiplicity of infection (MOI) of 0.1 to 10, more typically near 3. Procedures used are generally described in available laboratory manuals (e.g., King and Possee, *ibid.*; O'Reilly et al., *ibid.*; Richardson, *ibid.*). See also, Guarino et al., U.S. Patent No. 5,162,222 and WIPO publication WO 94/06463.

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Fungal cells, including yeast cells, can also be used within the present invention. Yeast species of particular interest in this regard include Saccharomyces cerevisiae, Pichia pastoris, and Pichia methanolica. Methods for transforming S. cerevisiae cells with exogenous DNA and producing recombinant polypeptides therefrom are disclosed by, for example, Kawasaki, U.S. Patent No. 4.599,311: Kawasaki et al., U.S. Patent No. 4,931,373; Brake, U.S. Patent No. 4,870,008; Welch et al., U.S. Patent No. 5,037,743; and Murray et al., U.S. Patent No. 4,845,075. Transformed cells are selected by phenotype determined by the selectable marker. commonly drug resistance or the ability to grow in the absence of a particular nutrient (e.g., leucine). A preferred vector system for use in Saccharomyces cerevisiae is the POT1 vector system disclosed by Kawasaki et al. (U.S. Patent No. 4,931,373), which allows transformed cells to be selected by growth in glucose-containing media. Suitable promoters and terminators for use in yeast include those from glycolytic enzyme genes (see, e.g., Kawasaki, U.S. Patent No. 4,599,311; Kingsman et al., U.S. Patent No. 4,615,974; and Bitter, U.S. Patent No. 4,977,092) and alcohol dehydrogenase genes. See also U.S. Patents Nos. 4,990,446; 5,063,154; 5,139,936 and 4,661,454.

Transformation systems for other yeasts, including Hansenula polymorpha, Schizosaccharomyces pombe, Kluyveromyces lactis, Kluyveromyces fragilis, Ustilago maydis, Pichia pastoris, Pichia methanolica, Pichia guillermondii and Candida maltosa are known in the art. See, for example, Gleeson et al., J. Gen. Microbiol. 132:3459-3465, 1986 and Cregg, U.S. Patent No. 4,882,279. Aspergillus cells may be utilized according to the methods of McKnight et al., U.S. Patent No. 4,935,349. Methods for transforming Acremonium chrysogenum are disclosed by Sumino et al., U.S. Patent No. 5,162,228. Methods for transforming Neurospora are disclosed by Lambowitz, U.S. Patent No. 4,486,533. Production of recombinant proteins in Pichia methanolica is disclosed in U.S. Patents No. 5,716,808, 5,736,383, 5,854,039, and 5,888,768; and WIPO publications WO 99/14347 and WO 99/14320.

Other higher eukaryotic cells, including plant cells and avian cells, can also be used as hosts according to methods commonly known in the art. For example, the use of *Agrobacterium rhizogenes* as a vector for expressing genes in plant cells has been reviewed by Sinkar et al., *J. Biosci.* (*Bangalore*) 11:47-58, 1987.

Prokaryotic host cells, including strains of the bacteria Escherichia coli, Bacillus and other genera are also useful host cells within the present invention. Techniques for transforming these hosts and expressing foreign DNA sequences cloned therein are well known in the art (see, e.g., Sambrook et al., ibid.). When expressing a polypeptide in bacteria such as E. coli, the polypeptide may be retained in the

thereby obviating the need for denaturation and refolding.

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cytoplasm, typically as insoluble granules, or may be directed to the periplasmic space by a bacterial secretion sequence. In the former case, the cells are lysed, and the granules are recovered and denatured using, for example, guanidine isothiocyanate or urea. The denatured polypeptide can then be refolded and dimerized by diluting the denaturant, such as by dialysis against a solution of urea and a combination of reduced and oxidized glutathione, followed by dialysis against a buffered saline solution. In the latter case, the polypeptide can be recovered from the periplasmic space in a soluble and functional form by disrupting the cells (by, for example, sonication or osmotic shock) to release the contents of the periplasmic space and recovering the protein,

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Transformed or transfected host cells are cultured according to conventional procedures in a culture medium containing nutrients and other components required for the growth of the chosen host cells. A variety of suitable media, including defined media and complex media, are known in the art and generally include a carbon source, a nitrogen source, essential amino acids, vitamins and minerals. Media may also contain such components as growth factors or serum, as required. The growth medium will generally select for cells containing the exogenously added DNA by, for example, drug selection or deficiency in an essential nutrient which is complemented by the selectable marker carried on the expression vector or co-transfected into the host cell.

It is preferred to purify the polypeptides and proteins of the present invention to ≥80% purity, more preferably to ≥90% purity, even more preferably ≥95% purity, and particularly preferred is a pharmaceutically pure state, that is greater than 99.9% pure with respect to contaminating macromolecules, particularly other proteins and nucleic acids, and free of infectious and pyrogenic agents. Preferably, a purified polypeptide or protein is substantially free of other polypeptides or proteins, particularly those of animal origin.

Expressed recombinant proteins (including single polypeptide chains, chimeric polypeptides, and polypeptide multimers) are purified by conventional protein purification methods, typically by a combination of chromatographic techniques. See, in general, Affinity Chromatography: Principles & Methods, Pharmacia LKB Biotechnology, Uppsala, Sweden, 1988; and Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York, 1994. Proteins comprising a polyhistidine affinity tag (typically about 6 histidine residues) are purified by affinity chromatography on a nickel chelate resin. See, for example, Houchuli et al., Bio/Technol. 6: 1321-1325, 1988. Proteins comprising a glu-glu tag can be purified by immunoaffinity chromatography essentially as disclosed by Grussenmeyer et al., ibid.

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Proteins comprising other affinity tags can be purified by appropriate affinity chromatography methods, which are known in the art.

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Proteins of the present invention and fragments thereof can also be prepared through chemical synthesis according to methods known in the art, including exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. See, for example, Merrifield, J. Am. Chem. Soc. 85:2149. 1963; Stewart et al., Solid Phase Peptide Synthesis (2nd edition), Pierce Chemical Co., Rockford, IL, 1984; Bayer and Rapp, Chem. Pept. Prot. 3:3, 1986; and Atherton et al., Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford, 1989.

Using methods known in the art, the proteins of the present invention can be prepared in a variety of modified or derivatized forms. For example, the proteins can be prepared glycosylated or non-glycosylated; pegylated or non-pegylated; and may or may not include an initial methionine amino acid residue.

Biological activities of the proteins of the present invention can be measured in vitro using cultured cells or in vivo by administering molecules of the claimed invention to the appropriate animal model. Many such assays and models are known in the art. Guidance in initial assay selection is provided by structural predictions and sequence alignments. However, even if no functional prediction is made, the activity of a protein can be elucidated by known methods, including, for example, screening a variety of target cells for a biological response, other in vitro assays, expression in a host animal, or through the use of transgenic and/or "knockout" animals. Through the application of robotics, many in vitro assays can be adapted to rapid, high-throughput screeing of a large number of samples. Target cells for use in activity assays include, without limitation, vascular cells (especially endothelial cells and smooth muscle cells), hematopoietic (myeloid and lymphoid) cells, liver cells (including hepatocytes, fenestrated endothelial cells, Kupffer cells, and Ito cells), fibroblasts (including human dermal fibroblasts and lung fibroblasts), neurite cells (including astrocytes, glial cells, dendritic cells, and PC-12 cells), fetal lung cells, articular synoviocytes, pericytes, chondrocytes, osteoblasts, adipocytes, and prostate epithelial cells. Endothelial cells and hematopoietic cells are derived from a common ancestral cell, the hemangioblast (Choi et al., Development 125:725-732, 1998).

Biological activity can be measured with a silicon-based biosensor microphysiometer that measures the extracellular acidification rate or proton excretion associated with receptor binding and subsequent physiologic cellular responses. An exemplary such device is the Cytosensor™ Microphysiometer manufactured by Molecular Devices, Sunnyvale, CA. A variety of cellular responses, such as cell proliferation, ion transport, energy production, inflammatory response, regulatory and

receptor activation, and the like, can be measured by this method. See, for example, McConnell et al., Science 257:1906-1912, 1992; Pitchford et al., Meth. Enzymol. 228:84-108, 1997; Arimilli et al., J. Immunol. Meth. 212:49-59, 1998; and Van Liefde et al., Eur. J. Pharmacol. 346:87-95, 1998. The microphysiometer can be used for assaying adherent or non-adherent eukaryotic or prokaryotic cells. By measuring extracellular acidification changes in cell media over time, the microphysiometer directly measures cellular responses to various stimuli, including agonistic and antagonistic stimuli. Preferably, the microphysiometer is used to measure responses of a eukaryotic cell known to be responsive to the protein of interest, compared to a control eukaryotic cell that does not respond to the protein of interest. Responsive eukaryotic cells comprise cells into which a receptor for the protein of interest has been transfected, as well as naturally responsive cells. Differences in the response of cells exposed to the protein of interest, relative to a control not so exposed, are a direct measurement of protein-modulated cellular responses. Such responses can be assayed under a variety of stimuli. The present invention thus provides methods of identifying agonists and antagonists of proteins of interest, comprising providing cells responsive to a selected protein, culturing a first portion of the cells in the absence of a test compound, culturing a second portion of the cells in the presence of a test compound, and detecting a change in a cellular response of the second portion of the cells as compared to the first portion of the cells. The change in cellular response is shown as a measurable change in extracellular acidification rate. Culturing a third portion of the cells in the presence of the protein of interest and the absence of a test compound provides a positive control and a control to compare the agonist activity of a test compound with that of the protein of interest. Antagonists can be identified by exposing the cells to the protein of interest in the presence and absence of the test compound, whereby a reduction in protein-stimulated activity is indicative of antagonist activity in the test compound.

Assays measuring cell proliferation or differentiation are well known in the art. For example, assays measuring proliferation include such assays as chemosensitivity to neutral red dye (Cavanaugh et al., Investigational New Drugs 8:347-354, 1990), incorporation of radiolabelled nucleotides (as disclosed by, e.g., Raines and Ross, Methods Enzymol. 109:749-773, 1985; Wahl et al., Mol. Cell Biol. 8:5016-5025, 1988; and Cook et al., Analytical Biochem. 179:1-7, 1989), incorporation of 5-bromo-2'-deoxyuridine (BrdU) in the DNA of proliferating cells (Porstmann et al., J. Immunol. Methods 82:169-179, 1985), and use of tetrazolium salts (Mosmann, J. Immunol. Methods 65:55-63, 1983; Alley et al., Cancer Res. 48:589-601, 1988; Marshall et al., Growth Reg. 5:69-84, 1995; and Scudiero et al., Cancer Res. 48:4827-

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4833, 1988). Differentiation can be assayed using suitable precursor cells that can be induced to differentiate into a more mature phenotype. Assays measuring differentiation include, for example, measuring cell-surface markers associated with stage-specific expression of a tissue, enzymatic activity, functional activity or morphological changes (Watt, FASEB, 5:281-284, 1991; Francis, Differentiation 57:63-75, 1994; Raes, Adv. Anim. Cell Biol. Technol. Bioprocesses, 161-171, 1989). Effects of a protein on tumor cell growth and metastasis can be analyzed using the Lewis lung carcinoma model, for example as described by Cao et al., J. Exp. Med. 182:2069-2077, 1995. Activity of a protein on cells of neural origin can be analyzed using assays that measure effects on neurite growth as disclosed below.

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In vitro assays for pro- and anti-inflammatory activity are known in the art. Exemplary activity assays include mitogenesis assays in which IL-1 responsive cells (e.g., D10.N4.M cells) are incubated in the presence of IL-1 or a test protein for 72 hours at 37°C in a 5% CO₂ atmosphere. IL-2 (and optionally IL-4) is added to the culture medium to enhance sensitivity and specificity of the assay. ³H-thymidine is then added, and incubation is continued for six hours. The amount of label incorporated is indicative of agonist activity. See, Hopkins and Humphreys, J. Immunol. Methods 120:271-276, 1989; Greenfeder et al., J. Biol. Chem. 270:22460-22466, 1995. Stimulation of cell proliferation can also be measured using thymocytes cultured in a test protein in combination with phytohemagglutinin. IL-1 is used as a control. Proliferation is detected as ³H-thymidine incorporation or metabolic breakdown of (MTT) (Mosman, ibid.).

Protein activity may also be detected using assays designed to measure induction of one or more growth factors or other macromolecules. Preferred such assays include those for determining the presence of hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factor alpha (TGFα), interleukin-6 (IL-6), VEGF, acidic fibroblast growth factor (aFGF), angiogenin, and other macromolecules produced by the liver. Suitable assays include mitogenesis assays using target cells responsive to the macromolecule of interest, receptor-binding assays, competition binding assays, immunological assays (e.g., ELISA), and other formats known in the art. Metalloprotease secretion is measured from treated primary human dermal fibroblasts, synoviocytes and chondrocytes. The relative levels of collagenase, gelatinase and stromalysin produced in response to culturing a target cell in the presence of a protein of interest is measured using zymogram gels (Loita and Stetler-Stevenson, *Cancer Biology* 1:96-106, 1990). Procollagen/collagen synthesis by dermal fibroblasts and chondrocytes in response to a test protein is measured using ³H-proline incorporation into nascent secreted collagen.

SDS-PAGE followed by autoradiography (Unemori and Amento, *J. Biol. Chem.* 265: 10681-10685, 1990). Glycosaminoglycan (GAG) secretion from dermal fibroblasts and chondrocytes is measured using a 1,9-dimethylmethylene blue dye binding assay (Farndale et al., *Biochim. Biophys. Acta* 883:173-177, 1986). Collagen and GAG assays are also carried out in the presence of IL-1β or TGF-β to examine the ability of a protein to modify the established responses to these cytokines.

Monocyte activation assays are carried out (1) to look for the ability of a protein of interest to further stimulate monocyte activation, and (2) to examine the ability of a protein of interest to modulate attachment-induced or endotoxin-induced monocyte activation (Fuhlbrigge et al., *J. Immunol.* 138: 3799-3802, 1987). IL-1 β and TNF α levels produced in response to activation are measured by ELISA (Biosource, Inc. Camarillo, CA). Monocyte/macrophage cells, by virtue of CD14 (LPS receptor), are exquisitely sensitive to endotoxin, and proteins with moderate levels of endotoxin-like activity will activate these cells.

Other metabolic effects of proteins can be measured by culturing target cells in the presence and absence of a protein and observing changes in adipogenesis, gluconeogenesis, glycogenolysis, lipogenesis, glucose uptake, or the like. Suitable assays are known in the art.

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Hematopoietic activity of proteins can be assayed on various hematopoietic cells in culture. Preferred assays include primary bone marrow colony assays and later stage lineage-restricted colony assays, which are known in the art (e.g., Holly et al., WIPO Publication WO 95/21920). Marrow cells plated on a suitable semi-solid medium (e.g., 50% methylcellulose containing 15% fetal bovine serum, 10% bovine serum albumin, and 0.6% PSN antibiotic mix) are incubated in the presence of test polypeptide, then examined microscopically for colony formation. Known hematopoietic factors are used as controls. Mitogenic activity of a protein of interest on hematopoietic cell lines can be measured as disclosed above.

Cell migration is assayed essentially as disclosed by Kähler et al. (Arteriosclerosis, Thrombosis, and Vascular Biology 17:932-939, 1997). A protein is considered to be chemotactic if it induces migration of cells from an area of low protein concentration to an area of high protein concentration. A typical assay is performed using modified Boyden chambers with a polystryrene membrane separating the two chambers (Transwell; Corning Costar Corp.). The test sample, diluted in medium containing 1% BSA, is added to the lower chamber of a 24-well plate containing Transwells. Cells are then placed on the Transwell insert that has been pretreated with 0.2% gelatin. Cell migration is measured after 4 hours of incubation at 37°C. Non-migrating cells are wiped off the top of the Transwell membrane, and cells

attached to the lower face of the membrane are fixed and stained with 0.1% crystal violet. Stained cells are then extracted with 10% acetic acid and absorbance is measured at 600 nm. Migration is then calculated from a standard calibration curve. Cell migration can also be measured using the matrigel method of Grant et al. ("Angiogenesis as a component of epithelial-mesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997).

Proteins can be assayed for the ability to modulate axon guidance and growth. Suitable assays that detect changes in neuron growth patterns include, for example, those disclosed in Hastings, WIPO Publication WO 97/29189 and Walter et al., Development 101:685-96, 1987. Assays to measure the effects on neuron growth are well known in the art. For example, the C assay (e.g., Raper and Kapfhammer, Neuron 4:21-9, 1990 and Luo et al., Cell 75:217-27, 1993) can be used to determine collapsing activity of a protein of interest on growing neurons. Other methods that can assess protein-induced inhibition of neurite extension or divert such extension are also known. See, Goodman, Annu. Rev. Neurosci. 19:341-77, 1996. Conditioned media from cells expressing a protein of interest, or aggregates of such cells, can by placed in a gel matrix near suitable neural cells, such as dorsal root ganglia (DRG) or sympathetic ganglia explants, which have been co-cultured with nerve growth factor. Compared to control cells, protein-induced changes in neuron growth can be measured (as disclosed by, for example, Messersmith et al., Neuron 14:949-59, 1995 and Puschel et al., Neuron 14:941-8, 1995). Neurite outgrowth can be measured using neuronal cell suspensions grown in the presence of molecules of the present invention. See, for example, O'Shea et al., Neuron 7:231-7, 1991 and DeFreitas et al., Neuron 15:333-43, 1995.

Cell adhesion activity is assayed essentially as disclosed by LaFleur et al. (*J. Biol. Chem.* 272:32798-32803, 1997). Briefly, microtiter plates are coated with the test protein, non-specific sites are blocked with BSA, and cells (such as smooth muscle cells, leukocytes, or endothelial cells) are plated at a density of approximately 10^4 - 10^5 cells/well. The wells are incubated at 37°C (typically for about 60 minutes), then non-adherent cells are removed by gentle washing. Adhered cells are quantitated by conventional methods (e.g., by staining with crystal violet, lysing the cells, and determining the optical density of the lysate). Control wells are coated with a known adhesive protein, such as fibronectin or vitronectin.

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Assays for angiogenic activity are also known in the art. For example, the effect of a protein of interest on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science

246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Other suitable assays include microinjection of early stage quail (Coturnix coturnix japonica) embryos as disclosed by Drake et al. (Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995); the rodent model of corneal neovascularization disclosed by Muthukkaruppan and Auerbach (Science 205:1416-1418, 1979), wherein a test substance is inserted into a pocket in the cornea of an inbred mouse; and the hampster cheek pouch assay (Höckel et al., Arch. Surg. 128:423-429, 1993). Induction of vascular permeability, which is indicative of angiogenic activity, is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, J. Physiol. 118:228-257, 1952; Feng et al., J. Exp. Med. 183:1981-1986, 1996). In vitro assays for angiogenic activity include the 15 tridimensional collagen gel matrix model (Pepper et al. Biochem. Biophys. Res. Comm. 189:824-831, 1992 and Ferrara et al., Ann. NY Acad. Sci. 732:246-256, 1995), which measures the formation of tube-like structures by microvascular endothelial cells; and matrigel models (Grant et al., "Angiogenesis as a component of epithelialmesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997), which are used to determine effects on cell migration and tube formation by endothelial cells seeded in matrigel, a basement membrane extract enriched in laminin. It is preferred to carry out angiogenesis assays in the presence and absence of vascular endothelial growth factor (VEGF) to assess possible combinatorial effects. It is also preferred to use VEGF as a control within in vivo assays.

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Receptor binding can be measured by the competition binding method of Labriola-Tompkins et al., Proc. Natl. Acad. Sci. USA 88:11182-11186, 1991. In an exemplary assay for IL-1 receptor binding, membranes pepared from EL-4 thymoma cells (Paganelli et al., J. Immunol. 138:2249-2253, 1987) are incubated in the presence of the test protein for 30 minutes at 37°C. Labeled IL-1α or IL-1β is then added and the incubation is continued for 60 minutes. The assay is terminated by membrane filtration. The amount of bound label is determined by conventional means (e.g., γ counter). In an alternative assay, the ability of a test protein to compete with labeled IL-1 for binding to cultured human dermal fibroblasts is measured according to the method of Dower et al. (Nature 324:266-268, 1986). Briefly, cells are incubated in a round-bottomed, 96-well plate in a suitable culture medium (e.g., RPMI 1640 containing 1% BSA, 0.1% Na azide, and 20 mM HEPES pH 7.4) at 8°C on a rocker

platform in the presence of labeled IL-1. Various concentrations of test protein are added. After the incubation (typically about two hours), cells are separated from unbound label by centrifuging 60-µl aliquots through 200 µl of phthalate oils in 400-µl polyethylene centrifuge tubes and excising the tips of the tubes with a razor blade as disclosed by Segal and Hurwitz, *J. Immunol.* 118:1338-1347, 1977. Receptor binding assays for other cell types are known in the art. See, for example, Bowen-Pope and Ross, *Methods Enzymol.* 109:69-100, 1985.

Receptor binding can also be measured using immobilized receptors or ligand-binding receptor fragments. For example, an immobilized receptor can be exposed to its labeled ligand and unlabeled test protein, whereby a reduction in labeled ligand binding compared to a control is indicative of receptor-binding activity in the test protein. Within another format, a receptor or ligand-binding receptor fragment is immobilized on a biosensor (e.g., BIACoreTM, Pharmacia Biosensor, Piscataway, NJ) and binding is determined. Antagonists of the native ligand will exhibit receptor binding but will exhibit essentially no activity in appropriate activity assays or will reduce the ligand-mediated response when combined with the native ligand. In view of the low level of receptor occupancy required to produce a response to some ligands (e.g., IL-1), a large excess of antagonist (typically a 10- to 1000-fold molar excess) may be necessary to neutralize ligand activity.

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Receptor activation can be detected in target cells by: (1) measurement of adenylate cyclase activity (Salomon et al., Anal. Biochem. 58:541-48, 1974; Alvarez and Daniels, Anal. Biochem. 187:98-103, 1990); (2) measurement of change in intracellular cAMP levels using conventional radioimmunoassay methods (Steiner et al., J. Biol. Chem. 247:1106-13, 1972; Harper and Brooker, J. Cyc. Nucl. Res. 1:207-18, 1975); or (3) through use of a cAMP scintillation proximity assay (SPA) method (such as available from Amersham Corp., Arlington Heights, IL).

Proteins can be tested for serine protease activity or proteinase inhibitory activity using conventional assays. Substrate cleavage is conveniently assayed using a tetrapeptide that mimics the cleavage site of the natural substrate and which is linked, via a peptide bond, to a carboxyl-terminal para-nitro-anilide (pNA) group. The protease hydrolyzes the bond between the fourth amino acid residue and the pNA group, causing the pNA group to undergo a dramatic increase in absorbance at 405 nm. Suitable substrates can be synthesized according to known methods or obtained from commercial suppliers. Inhibitory activity is measured by adding a test sample to a reaction mixture containing enzyme and substrate, and comparing the observed enzyme activity to a control (without the test sample). A variety of such assays are known in the art, including assays measuring inhibition of trypsin,

chymotrypsin, plasmin, cathepsin G, and human leukocyte elastase. See, for example, Petersen et al., Eur. J. Biochem. 235:310-316, 1996. In a typical procedure, the inhibitory activity of a test compound is measured by incubating the test compound with the proteinase, then adding an appropriate substrate, typically a chromogenic peptide substrate. See, for example, Norris et al. (Biol. Chem. Hoppe-Seyler 371:37-42, 1990). Various concentrations of the inhibitor are incubated in the presence of trypsin, plasmin, and plasma kallikrein in a low-salt buffer at pH 7.4, 25°C. After 30 minutes, the residual enzymatic activity is measured by the addition of a chromogenic substrate (e.g., S2251 (D-Val-Leu-Lys-Nan) or S2302 (D-Pro-Phe-Arg-Nan), available from Kabi, Stockholm, Sweden) and a 30-minute incubation. Inhibition of enzyme activity is indicated by a decrease in absorbance at 405 nm or fluorescence Em at 460 nm. From the results, the apparent inhibition constant K_i is calculated. When a serine protease is prepared as an active precursor (e.g., comprising N-terminal residues 1-109 of SEQ ID NO:2), it is activated by cleavage with a suitable protease (e.g., furin (Steiner et al., <u>J. Biol. Chem.</u> 267:23435-23438, 1992)) prior to assay. Assays of this type are well known in the art. See, for example, Lottenberg et al., Thrombosis Research 28:313-332, 1982; Cho et al., Biochem. 23:644-650, 1984; Foster et al., Biochem. 26:7003-7011, 1987). The inhibition of coagulation factors (e.g., factor VIIa, factor Xa) can be measured using chromogenic substrates or in conventional coagulation assays (e.g., clotting time of normal human plasma; Dennis et al., J. Biol. Chem. <u>270</u>:25411-25417, 1995).

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Blood coagulation and chromogenic assays, which can be used to detect both procoagulant, anticoagulant, and thrombolytic activities, are known in the art. For example, pro- and anticoagulant activities can be measured in a one-stage clotting assay using platelet-poor or factor-deficient plasma (Levy and Edgington, *J. Exp. Med.* 151:1232-1243, 1980; Schwartz et al., *J. Clin. Invest.* 67:1650-1658, 1981). As disclosed by Anderson et al. (*Proc. Natl. Acad. Sci. USA* 96:11189-11193, 1999), the effect of a test compound on platelet activation can be determined by a change in turbidity, and the procoagulant activity of activated platelets can be determined in a phospholipid-dependent coagulation assay. Activation of thrombin can be determined by hydrolysis of peptide p-nitroanilide substrates as disclosed by Lottenberg et al. (*Thrombosis Res.* 28:313-332, 1982). Other procoagulant, anticoagulant, and thrombolytic activities can be measured using appropriate chromogenic substrates, a variety of which are available from commercial suppliers. See, for example, Kettner and Shaw, *Methods Enzymol.* 80:826-842, 1981.

Anti-microbial activity of proteins is evaluated by techniques that are known in the art. For example, anti-microbial activity can be assayed by evaluating the

sensitivity of microbial cell cultures to test agents and by evaluating the protective effect of test agents on infected mice. See, for example, Musiek et al., Antimicrob. Agents Chemothr. 3:40, 1973. Antiviral activity can also be assessed by protection of mammalian cell cultures. Known techniques for evaluating anti-microbial activity include, for example, Barsum et al., Eur. Respir. J. 8:709-714, 1995; Sandovsky-Losica et al., J. Med. Vet. Mycol (England) 28:279-287, 1990; Mehentee et al., J. Gen. Microbiol (England) 135(:2181-2188, 1989; and Segal and Savage, J. Med. Vet. Mycol. 24:477-479, 1986. Assays specific for anti-viral activity include, for example, those described by Daher et al., J. Virol. 60:1068-1074, 1986.

The assays disclosed above can be modified by those skilled in the art to detect the presence of agonists and antagonists of a selected protein of interest.

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Expression of a polynucleotide encoding a protein of interest in animals provides models for further study of the biological effects of overproduction or inhibition of protein activity *in vivo*. Polynucleotides and antisense polynucleotides can be introduced into test animals, such as mice, using viral vectors or naked DNA, or transgenic animals can be produced.

One *in vivo* approach for assaying proteins of the present invention utilizes viral delivery systems. Exemplary viruses for this purpose include adenovirus, herpesvirus, retroviruses, vaccinia virus, and adeno-associated virus (AAV). Adenovirus, a double-stranded DNA virus, is currently the best studied gene transfer vector for delivery of heterologous nucleic acids. For review, see Becker et al., *Meth. Cell Biol.* 43:161-89, 1994; and Douglas and Curiel, *Science & Medicine* 4:44-53, 1997. The adenovirus system offers several advantages. Adenovirus can (i) accommodate relatively large DNA inserts; (ii) be grown to high-titer; (iii) infect a broad range of mammalian cell types; and (iv) be used with many different promoters including ubiquitous, tissue specific, and regulatable promoters. Because adenoviruses are stable in the bloodstream, they can be administered by intravenous injection.

By deleting portions of the adenovirus genome, larger inserts (up to 7 kb) of heterologous DNA can be accommodated. These inserts can be incorporated into the viral DNA by direct ligation or by homologous recombination with a cotransfected plasmid. In an exemplary system, the essential E1 gene is deleted from the viral vector, and the virus will not replicate unless the E1 gene is provided by the host cell (e.g., the human 293 cell line). When intravenously administered to intact animals, adenovirus primarily targets the liver. If the adenoviral delivery system has an E1 gene deletion, the virus cannot replicate in the host cells. However, the host's tissue (e.g., liver) will express and process (and, if a signal sequence is present, secrete) the

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heterologous protein. Secreted proteins will enter the circulation in the highly vascularized liver, and effects on the infected animal can be determined.

An alternative method of gene delivery comprises removing cells from the body and introducing a vector into the cells as a naked DNA plasmid. The transformed cells are then re-implanted in the body. Naked DNA vectors are introduced into host cells by methods known in the art, including transfection, electroporation, microinjection, transduction, cell fusion, DEAE dextran, calcium phosphate precipitation, use of a gene gun, or use of a DNA vector transporter. See, Wu et al., J. Biol. Chem. 263:14621-14624, 1988; Wu et al., J. Biol. Chem. 267:963-10 967, 1992; and Johnston and Tang, Meth. Cell Biol. 43:353-365, 1994.

Transgenic mice, engineered to express a gene encoding a protein of interest, and mice that exhibit a complete absence of gene function, referred to as "knockout mice" (Snouwaert et al., Science 257:1083, 1992), can also be generated (Lowell et al., Nature 366:740-742, 1993). These mice can be employed to study the 15 gene of interest and the protein encoded thereby in an in vivo system. Transgenic mice are particularly useful for investigating the role of proteins in early development in that they allow the identification of developmental abnormalities or blocks resulting from the over- or underexpression of a specific factor. See also, Maisonpierre et al., Science 277:55-60, 1997 and Hanahan, Science 277:48-50, 1997. Preferred promoters for transgenic expression include promoters from metallothionein and albumin genes. As disclosed above, the human sequences provided herein can be used to clone orthologous polynucleotides, which may be preferred for use in generating transgenic and knockout animals.

Antisense methodology can be used to inhibit gene transcription to examine the effects of such inhibition in vivo. Polynucleotides that are complementary to a segment of a protein-encoding polynucleotide are designed to bind to the encoding mRNA and to inhibit translation of such mRNA. Such antisense oligonucleotides can also be used to inhibit expression of protein-encoding genes in cell culture.

Biological activities of test proteins can also be measured in animal models by administering the test protein, by itself or in combination with other agents, including other proteins. Using such models facilitates the assay of the test protein by itself or as an inhibitor or modulator of another agent, and also facilitates the measurement of combinatorial effects of bioactive compounds.

Anti-inflammatory activity can be tested in animal models of inflammatory disease. For example, animal models of psoriasis include the analysis of histological alterations in adult mouse tail epidermis (Hofbauer et al, Brit. J. Dermatol.

118:85-89, 1988; Bladon et al., Arch Dermatol. Res. 277:121-125, 1985). In this model, anti-psoriatic activity is indicated by the induction of a granular layer and orthokeratosis in areas of scale between the hinges of the tail epidermis. Typically, a topical ointment comprising a test compound is applied daily for seven consecutive days, then the animal is sacrificed, and tail skin is examined histologically. An additional model is provided by grafting psoriatic human skin to congenitally athymic (nude) mice (Krueger et al., J. Invest. Dermatol. 64:307-312, 1975). Such grafts have been shown to retain the characteristic histology for up to eleven weeks. As in the mouse tail model, the test composition is applied to the skin at predetermined intervals for a period of one to several weeks, at which time the animals are sacrificed and the skin grafts examined histologically. A third model has been disclosed by Fretland et al. (Inflammation 14:727-739, 1990). Briefly, inflammation is induced in guinea pig epidermis by topically applying phorbol ester (phorbol-12-myristate-13-acetate; PMA), typically at ca. 2 g/ml in acetone, to one ear and vehicle to the contralateral ear. Test compounds are applied concurrently with the PMA, or may be given orally. Histological analysis is performed at 96 hours after application of PMA. This model duplicates many symptoms of human psoriasis, including edema, inflammatory cell diapedesis and infiltration, high LTB₄ levels and epidermal proliferation.

Cerebral ischemia can be studied in a rat model as disclosed by Relton 20 et al. (*ibid.*) and Loddick et al. (*ibid.*).

The effect of a test protein on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science 246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Embryo microinjection of early stage quail (Coturnix coturnix japonica) embryos can also be used (Drake et al., Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995). Briefly, a solution containing the protein is injected into the interstitial space between the endoderm and the splanchnic mesoderm of early-stage embryos using a micropipette and micromanipulator system. After injection, embryos are placed ventral side down on a nutrient agar medium and incubated for 7 hours at 37°C in a humidified CO₂/air mixture (10%/90%). Vascular development is assessed by microscopy of fixed, whole-mounted embryos and sections.

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Stimulation of coronary collateral growth can be measured in known animal models, including a rabbit model of peripheral limb ischemia and hind limb ischemia and a pig model of chronic myocardial ischemia (Ferrara et al., *Endocrine*

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Reviews 18:4-25, 1997). Test proteins are assayed in the presence and absence of VEGF and basic FGF to test for combinatorial effects. These models can be modified by the use of adenovirus or naked DNA for gene delivery as disclosed in more detail above, resulting in local expression of the test protein(s).

Angiogenic activity can also be tested in a rodent model of corneal neovascularization as disclosed by Muthukkaruppan and Auerbach, *Science* 205:1416-1418, 1979, wherein a test substance is inserted into a pocket in the cornea of an inbred mouse. For use in this assay, proteins are combined with a solid or semi-solid, biocompatible carrier, such as a polymer pellet. Angiogenesis is followed microscopically. Vascular growth into the corneal stroma can be detected in about 10 days.

Angiogenic activity can also be tested in the hampster cheek pouch assay (Höckel et al., *Arch. Surg.* 128:423-429, 1993). A test substance is injected subcutaneiously into the cheek pouch, and after five days the pouch is examined under low magnification to determine the extent of neovascularization. Tissue sections can also be examined histologically.

Induction of vascular permeability is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, *J. Physiol.* 118:228-257, 1952; Feng et al., *J. Exp. Med.* 183:1981-1986, 1996).

Wound-healing models include the linear skin incision model of Mustoe et al. (Science 237:1333, 1987). In a typical procedure, a 6-cm incision is made in the dorsal pelt of an adult rat, then closed with wound clips. Test substances and controls (in solution, gel, or powder form) are applied before primary closure. It is preferred to limit administration to a single application, although additional applications can be made on succeeding days by careful injection at several sites under the incision. Wound breaking strength is evaluated between 3 and 21 days post wounding. In a second model, multiple, small, full-thickness excisions are made on the ear of a rabbit. The cartilage in the ear splints the wound, removing the variable of wound contraction from the evaluation of closure. Experimental treatments and controls are applied. The geometry and anatomy of the wound site allow for reliable quantification of cell ingrowth and epithelial migration, as well as quantitative analysis of the biochemistry of the wounds (e.g., collagen content). See, Mustoe et al., J. Clin. Invest. 87:694, 1991. The rabbit ear model can be modified to create an ischemic wound environment. which more closely resembles the clinical situation (Ahn et al., Ann. Plast. Surg. 24:17, 1990). Within a third model, healing of partial-thickness skin wounds in pigs or guinea pigs is evaluated (LeGrand et al., Growth Factors 8:307, 1993). Experimental

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treatments are applied daily on or under dressings. Seven days after wounding, granulation tissue thickness is determined. This model is preferred for dose-response studies, as it is more quantitative than other in vivo models of wound healing. A full thickness excision model can also be employed. Within this model, the epidermis and dermis are removed down to the panniculus carnosum in rodents or the subcutaneous fat in pigs. Experimental treatments are applied topically on or under a dressing, and can be applied daily if desired. The wound closes by a combination of contraction and cell ingrowth and proliferation. Measurable endpoints include time to wound closure. histologic score, and biochemical parameters of wound tissue. Impaired wound healing models are also known in the art (e.g., Cromack et al., Surgery 113:36, 1993; Pierce et al., Proc. Natl. Acad. Sci. USA 86:2229, 1989; Greenhalgh et al., Amer. J. Pathol. 136:1235, 1990). Delay or prolongation of the wound healing process can be induced pharmacologically by treatment with steroids, irradiation of the wound site, or by concomitant disease states (e.g., diabetes). Linear incisions or full-thickness 15 excisions are most commonly used as the experimental wound. Endpoints are as disclosed above for each type of wound. Subcutaneous implants can be used to assess compounds acting in the early stages of wound healing (Broadley et al., Lab. Invest. 61:571, 1985; Sprugel et al., Amer. J. Pathol. 129: 601, 1987). Implants are prepared in a porous, relatively non-inflammatory container (e.g., polyethylene sponges or expanded polytetrafluoroethylene implants filled with bovine collagen) and placed subcutaneously in mice or rats. The interior of the implant is empty of cells, producing a "wound space" that is well-defined and separable from the preexisting tissue. This arrangement allows the assessment of cell influx and cell type as well as the measurement of vasculogenesis/angiogenesis and extracellular matrix production.

Inhibition of tumor metastasis can be assessed in mice into which cancerous cells or tumor tissue have been introduced by implantation or injection (e.g., Brown, Advan. Enzyme Regul. 35:293-301, 1995; Conway et al., Clin. Exp. Metastasis <u>14</u>:115-124, 1996).

Effects on fibrinolysis can be measured in a rat model wherein the enzyme batroxobin and radiolabeled fibrinogen are administered to test animals. Inhibition of fibrinogen activation by a test compound is seen as a reduction in the circulating level of the label as compared to animals not receiving the test compound. See, Lenfors and Gustafsson, Semin. Thromb. Hemost. 22:335-342, 1996.

The invention further provides polypeptides that comprise an epitope-35 bearing portion of a protein as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 436. An "epitope" is a region of a protein to which an antibody can bind. See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002, 1984.

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Epitopes can be linear or conformational, the latter being composed of discontinuous regions of the protein that form an epitope upon folding of the protein. Linear epitopes are generally at least 6 amino acid residues in length. Relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for example, Sutcliffe et al., Science 219:660-666, 1983. Antibodies that recognize short, linear epitopes are particularly useful in analytic and diagnostic applications that employ denatured protein, such as Western blotting (Tobin, Proc. Natl. Acad. Sci. USA 76:4350-4356, 1979). Antibodies to short peptides may also recognize proteins in native conformation and will thus be useful for monitoring protein expression and protein isolation, and in detecting proteins in solution, such as by ELISA or in immunoprecipitation studies.

Antigenic, epitope-bearing polypeptides of the present invention are useful for raising antibodies, including monoclonal antibodies, that specifically bind to the corresponding protein. Antigenic, epitope-bearing polypeptides contain a sequence of at least six, preferably at least nine, more preferably from 15 to about 30 contiguous amino acid residues of a protein. Within certain embodiments of the invention, the polypeptides comprise 40, 50, 100, or more contiguous residues of a protein as shown in SEQ ID NO:M, up to the entire predicted mature protein or the primary translation product. It is preferred that the amino acid sequence of the epitope-bearing polypeptide is selected to provide substantial solubility in aqueous solvents, that is the sequence includes relatively hydrophilic residues, and hydrophobic residues are substantially avoided. Table 10 lists preferred hexapeptides for use as antigens. Within Table 10, each the amino termini of the hexapeptides are specified. Those skilled in the art will recognize that longer polypeptides comprising these hexapeptides can also be used and will often be preferred.

		<u>Ta</u>	<u>ble 10</u>		
Protein		<u>Hexa</u>	peptide N	-termini	
AFP210015	389	405	97	388	359
AFP170681	51	334	113	49	140
AFP413680	221	207	220	206	198
AFP483037	219	218	82	216	215
AFP230872	189	188	73	156	68
AFP178828	211	210	209	208	207
AFP200134	150	149	146	132	145
AFP195796	99	97	111	208	240

AFP477303	64	126	63	54	112
AFP354334	269	268	267	266	265
AFP250287	34	33	48	2	143
AFP177000	133	132	104	37	68
AFP278176	234	145	.284	91	291
AFP202885	134	244	170	133	243
AFP221312	31	29	28	51	43
AFP239757	329	200	556	107	328
AFP226311	293	74	250	86	184
AFP305901	340	194	451	192	120
AFP325549	293	74	250	86	184
AFP81988	151	167	147	165	173
AFP199200	150	149	148	92	147
AFP290395	31	29	28	329	326
AFP212675	67	66	65	204	396
AFP326051	49	56	23	78	95
AFP512441	94	93	41	39	· 38
AFP55098	140	34 .	139	120	32
AFP169796	177	173	156	32	155
AFP280706	33	54	32	31	53
AFP383165	25	82	52	24	178
AFP195467	113	112	71	2	80
AFP134225	114	280	113	455	417
AFP261193	120	66	65	85	119
AFP324422	147	145	66	65	85
AFP374312	125	124	79	123	77
AFP258118	64	63	116	115	62
AFP74517	1	72	124	123	22
AFP254653	134	36	62	14	23
AFP108666	79	76	74	49	48
AFP8766	140	34	139	120	298
AFP397185	265	35	264	34	48
AFP195042	192	535	191	259	533
AFP310695	49	75	190	5	94
AFP70022	38	64	179	83	37
AFP121670	184	183	121	118	182
AFP345861	151	89	75	135	149

AFP395942	60	14	59	13	21
AFP170291	144	72	56	55	63
AFP297548	145	73	57	56	64
AFP188135	152	148	158	147	144
AFP302388	478	431	416	414	429
AFP263430	92	23	64	91	110
AFP201273	373	384	163	372	44
AFP98983	3	2	35	34	32
AFP581958	71	66	80	26	25
AFP404202	1	31	115	30	92
AFP207203	427	258	204	426	48
AFP220790	139	92	51	187	91
AFP536326	87	146	105	73	103
AFP257473	270	205	203	245	244
AFP248380	283	62	54	272	100
AFP276202	50	48	35	46	33
AFP227568	199	23	238	363	224
AFP229039	226	91	116	161	225
AFP176297	261	382	183	119	182
AFP356885	622	45	525	175	466
AFP226938	118	108	117	79	107
AFP138504	77	255	75	254	292
AFP359196	4	76	3	2	37
AFP501809	141	139	9	169	2
AFP152733	258	204	48	47	257
AFP541394	31	29	28	235	232
AFP243183	272	110	106	3	2
AFP80739	398	397	224	223	155
AFP361806	4	78	139	3	76
AFP483930	107	124	123	88	45
AFP257336	124	42	122	182	158
AFP195800	40	39	65	38	96
AFP179530	57	251	249	315	55
AFP279267	106	62	216	187	59
AFP299766	127	168	165	29	126
AFP244615	171	196	326	255	179
AFP325761	138	137	2	144	109

AFP226024	79	317	159	140	45
AFP257094	71	116	115	3	144
AFP197103	200	198	215	195	177
AFP271855	92	44	42	. 18	27
AFP324816	9	252	120	8	63
AFP407963	202	201	156	200	155
AFP369635	98	398	255	97	254
AFP93743	4	254	3	294	293
AFP243230	28	129	128	127	44
AFP169316	294	170	293	36	157
AFP130852	82	59	117	145	66
AFP194191	363	112	271	69	267
AFP213472	103	102	69	2	37
AFP360430	177	75	183	74	130
AFP491309	107	106	69 .	2	37
AFP193428	129	87	343	60	128
AFP366534	72	4	2	59	39
AFP22706	229	227	65	64	188
AFP389012	216	27	289	34	17
AFP137186	2	1	182	216	43
AFP127023	86	56	131	178	55
AFP389687	57	56	117	370	369
AFP293220	186	194	105	146	182
AFP425535	264	181	163	370	149
AFP301494	159	4	2	84	25
AFP345421	500	592	639	652	849
AFP216667	92	435	329	422	47
AFP247951	27	34	33	25	94
AFP4464	365	363	362	55	209
AFP561930	108	107	104	52	66
AFP192851	300	276	299	298	496
AFP252759	311	310	64	21	157
AFP199044	143	2	209	206	125
AFP357958	167	338	165	324	362
AFP117501	135	87	362	86	418
AFP194554	318	170	54	105	169
AFP371069	332	1	283	365	279

AFP313600	341	340	240	48	176
AFP262739	25	24	142	23	207
AFP180730	58	37	30	27	36
AFP287227	596	. 592	591	374	525
AFP75785	128	127	136	99	71
AFP174843	152	323	150	309	347
AFP250422	100	140	99	138	182
AFP198645	145	144	143	64	56
AFP238111	123	50	20	137	35
AFP460626	153	151	71	150	70
AFP271081	68	112	39	202	67
AFP277752	109	106	220	238	92
AFP291338	347	342	97	362	339
AFP551038	134	131	186	130	173
AFP301579	105	153	130	152	67
AFP266188	121	235	61	180	120
AFP275580	193	77	192	2	148
AFP298054	148	234	146	233	144
AFP348226	148	103	85	309	59
AFP349106	208	118	117	207	116
AFP288248	376	342	340	339	312
AFP436476	18	39	139	38	99
AFP352125	53	59	163	142	104
AFP62060	247	187	73	426	72
AFP236718	100	99	249	248	184
AFP75775	201	90	239	173	199
AFP407487	148	103	85	59	58
AFP280451	141	294	6	209	139
AFP11675	58	56	90	64	89
AFP348656	160	159	158	103	149
AFP277451	118	2	1	146	241
AFP287436	53	59	223	142	104
AFP116043	212	239	138	186	183
AFP138740	264	263	31	72	232
AFP15192	47	46	216	85	212
AFP169968	64	117	63	2	81
AFP173341	65	64	102	101	100

AFP17588	43	42	2	41	1
AFP176427	311	290	308	155	288
AFP192633	58	56	162	349	44
AFP193013	47	90	87	46	68
AFP193881	274	295	402	273	292
AFP195562	274	295	339	473	273
AFP199922	57	55	74	180	50
AFP204736	89	58	43	28	23
AFP206179	74	80	73	71	70
AFP221877	32	31	30	50	75
AFP222758	44	43	75	42	19
AFP227032	47	55	46	65	54
AFP229269	147	127	146	63	60
AFP232213	44	41	28 .	27	40
AFP237679	2	1	34	58	55
AFP249599	48	47	45	43	42
AFP275215	82	80	70	2	55
AFP290397	149	148	2	1	29
AFP306591	45	44	84	83	65
AFP310297	23	31	37	47	30
AFP314720	47	44	26	25	23
AFP318671	55	54	51	64	63
AFP323575	75	73	72	70	18
AFP327160	37	68	47	67	96
AFP329002	78	77	76	75	74
AFP345415	41	40	133	106	39
AFP347179	30	4	29	86	177
AFP359138	77	2	76	75	74
AFP365372	13	1	62	69	79
AFP367284	61	60	36	5	59
AFP372822	49	48	25	8	24
AFP374595	154	153	165	3	56
AFP375952	36	35	53	52	69
AFP382913	67	32	30	20	66
AFP389184	24	31	78	30	39
AFP404208	69	68	67	39	36
AFP404279	81	31	72	30	62

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AFP409112	97	96	56	94	55
AFP413111	65	85	96	64	94
AFP415635	35	26	25	34	32
AFP421092	27	1	46	57	35
AFP436666	5	95	59	4	58
AFP448623	14				
AFP454192	106	104	83	114	112
AFP49026	49	104	76	48	138
AFP51688	51	86	50	85	43
AFP525341	18	17	16	79	14
AFP545268	65	64	75	21	74
AFP592620	22	21	29	20	28
AFP62197	134	84	133	20	104
AFP68229	161	171	192	170	232
AFP71288	67	49	65	48	46
AFP77851	123	121	33	103	53
AFP81957	89	66	63	25	40
AFP85168	61	31	39	27	46

As used herein, the term "antibodies" includes polyclonal antibodies, monoclonal antibodies, antigen-binding fragments thereof such as F(ab')2 and Fab fragments, single chain antibodies, and the like, including genetically engineered 5 antibodies. Non-human antibodies can be humanized by grafting only non-human CDRs onto human framework and constant regions, or by incorporating the entire nonhuman variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced. One skilled in the art can generate humanized antibodies with specific and different constant domains (i.e., different Ig subclasses) to facilitate or inhibit various immune functions associated with particular antibody constant domains.

Alternative techniques for generating or selecting antibodies useful herein include in vitro exposure of lymphocytes to an immunogenic polypeptide, and selection of antibody display libraries in phage or similar vectors (for instance, through use of an immobilized or labeled polypeptide). Human antibodies can be produced in

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transgenic, non-human animals that have been engineered to contain human immunoglobulin genes as disclosed in WIPO Publication WO 98/24893. It is preferred that the endogenous immunoglobulin genes in these animals be inactivated or eliminated, such as by homologous recombination.

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Antibodies are defined to be specifically binding if they bind to a target polypeptide with an affinity at least 10-fold greater than the binding affinity to control (non-target) polypeptide. It is preferred that the antibodies exhibit a binding affinity (K_a) of 10⁶ M⁻¹ or greater, preferably 10⁷ M⁻¹ or greater, more preferably 10⁸ M⁻¹ or greater, and most preferably 10⁹ M⁻¹ or greater. The affinity of a monoclonal antibody can be readily determined by one of ordinary skill in the art (see, for example, Scatchard, *Ann. NY Acad. Sci.* 51: 660-672, 1949).

Methods for preparing polyclonal and monoclonal antibodies are well known in the art (see for example, Hurrell, J. G. R., Ed., Monoclonal Hybridoma Antibodies: Techniques and Applications, CRC Press, Inc., Boca Raton, FL, 1982). As would be evident to one of ordinary skill in the art, polyclonal antibodies can be generated from a variety of warm-blooded animals such as horses, cows, goats, sheep, dogs, chickens, rabbits, mice, and rats. The immunogenicity of a polypeptide immunogen may be increased through the use of an adjuvant such as alum (aluminum hydroxide) or Freund's complete or incomplete adjuvant. Polypeptides useful for immunization also include fusion polypeptides, such as fusions of a polypeptide of interest or a portion thereof with an immunoglobulin polypeptide or with maltose binding protein. The polypeptide immunogen may be a full-length molecule or a portion thereof. If the polypeptide portion is "hapten-like", such portion may be advantageously joined or linked to a macromolecular carrier (such as keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or tetanus toxoid) for immunization.

A variety of assays known to those skilled in the art can be utilized to detect antibodies that specifically bind to a polypeptide of interest. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.), Cold Spring Harbor Laboratory Press, 1988. Representative examples of such assays include concurrent immunoelectrophoresis, radio-immunoassays, radio-immunoprecipitations, enzyme-linked immunosorbent assays (ELISA), dot blot assays, Western blot assays, inhibition or competition assays, and sandwich assays.

Antibodies can be used, for example, to isolate target polypeptides by affinity purification, for diagnostic assays for determining circulating or localized levels of target polypeptides, for tissue typing, for cell sorting, for screening expression libraries; for generating anti-idiotypic antibodies, and as neutralizing antibodies or as antagonists to block protein activity in vitro and in vivo.

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The present invention also provides reagents for use in diagnostic and therapeutic applications. Such reagents include polynucleotide probes and primers; antibodies, including antibody fragments, single-chain antibodies, and other genetically engineered forms; soluble receptors and other polypeptide binding partners; and the proteins of the invention themselves, including fragments thereof. Those skilled in the art will recognize that diagnostic reagents will commonly be labeled to provide a detectable signal or other second function. Thus, polypeptides, antibodies, receptors, and other binding partners disclosed herein can be directly or indirectly conjugated to drugs, toxins, radionuclides, enzymes, enzyme substrates, cofactors, inhibitors, fluorescent markers, chemiluminescent markers, magnetic particles, and the like, and these conjugates used for in vivo diagnostic or therapeutic applications. Cytotoxic molecules, for example, can be directly or indirectly attached to the binding partner (e.g., by chemical coupling or as a fusion protein), and include bacterial or plant toxins (e.g., diphtheria toxin, Pseudomonas exotoxin, ricin, saporin, abrin, and the like); therapeutic radionuclides (e.g., iodine-131, rhenium-188 or yttrium-90) which can be directly attached to a polypeptide or antibody or indirectly attached through means of a chelating moiety; and cytotoxic drugs (e.g., adriamycin). Methods for preparing labeled reagents are known in the art. Within an alternative embodiment, the detectable signal or other function can be provided by a second member of a complement-anticomplement pair, which second member binds to the diagnostic reagent. For example, a first (unlabeled) antibody can be used to bind to a cell-surface polypeptide, after which a second, labeled antibody which binds to the first antibody is added. Other complement-anticomplement pairs are known in the art and include biotin/streptavidin.

Diagnostic reagents as disclosed herein can be used *in vivo* or *in vitro*. In vitro diagnostic assays include assays of tissue and fluid samples. Assays for protein in serum, for example, may be used to detect metabolic abnormalities characterized by over- or under-production of the protein, such as cancers, immune system abnormalities, infections, organ failure, metabolic imbalances, inborn errors of metabolism and other disease states. Proteins of the present invention can also be used in the detection of circulating autoantibodies, which are indicative of autoimmune disorders. Those skilled in the art will recognize that conditions related to protein underexpression or overexpression may be amenable to treatment by therapeutic manipulation of the relevant protein level(s). Proteins in serum can be quantitated by known methods known in the art, which include the use of antibodies in a variety of formats. Non-antibody binding partners, such as ligand-binding receptor fragments (commonly referred to as "soluble receptors") can also be used.

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In general, diagnostic methods employing oligonucleotide probes or primers comprise the steps of (a) obtaining a genetic sample from a patient; (b) incubating the genetic sample with an oligonucleotide probe or primer as disclosed above, under conditions wherein the probe or primer will hybridize to a complementary polynucleotide sequence, to produce a first reaction product; and (c) comparing the first reaction product to a control reaction product. A difference between the first reaction product and the control reaction product is indicative of a genetic abnormality in the patient. Genetic samples for use within such methods include genomic DNA, cDNA, and RNA. Suitable assay methods in this regard include molecular genetic techniques known to those in the art, such as restriction fragment length polymorphism (RFLP) analysis, short tandem repeat (STR) analysis employing PCR techniques, ligation chain reaction (Barany, PCR Methods and Applications 1:5-16, 1991), ribonuclease protection assays, and other genetic linkage analysis techniques known in the art (Sambrook et al., ibid.; Ausubel et. al., ibid.; A.J. Marian, Chest 108:255-65, 1995). Ribonuclease protection assays (see, e.g., Ausubel et al., ibid., ch. 4) comprise the hybridization of an RNA probe to a patient RNA sample, after which the reaction product (RNA-RNA hybrid) is exposed to RNase. Hybridized regions of the RNA are protected from digestion. Within PCR assays, a patient genetic sample is incubated with a pair of oligonucleotide primers, and the region between the primers is amplified and recovered. Changes in size, amount, or sequence of recovered product are indicative of mutations in the patient. Another PCR-based technique that can be employed is single strand conformational polymorphism (SSCP) analysis (Hayashi, PCR Methods and Applications 1:34-38, 1991). Chromosomal localization data can be used to correlate AFP gene locations with known genetic disorders using, for example, the OMIMTM Database, **Johns** Hopkins University, 2000 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

Relative chromosomal sublocalization shown in Table 11 was determined using the Draft Human Genome Browser (Kent, J., University of California Santa Cruz, http://genome.ucsc.edu/goldenPath/hgTracks.html) displaying the draft assembly of the July 17, 2000 version of the human genome. Table 11 also correlates AFP sequences with corresponding sequences in public databases by GenBank Accession Number, source clone ID number, and EST accession number. Also see Table 5, above.

			T	Table 11			
AFP	GenBank Acc. No.	Source Clone ID No.	EST Acc. No.	Chr.	Band	Start	Stop
AFP127023	AP001155	RP11-594B10	*	-88	18q12	35729370	35952786
AFP138504	AP001931	RP11-691N7	*	=	11p11.11	53438038	53888802
AFP138740	AC024059	RP11-79j21	AW580814	15	15q22.1	58185489	58481462
AFP138740	*	*	AW580814	15		58258653	58308652
AFP177000	AL118506	RP4-591C20	*	20	20q12	48950838	49160243
AFP178828	AC007686	CTD-2289B16;RP11-	*	14	14q23.3	62132030	62313415
		116N21;RP11-7F17					
AFP179530	AC011475	CTC-539A10	*	12	12q12	41234876	41456630
AFP188135	AC013740	*	*	6	9q31.2	91150313	91361876
AFP194554	AC024888	RP11-901L	*	16	16q22.1	71944378	72167142
AFP199044	AC012180	RP11-31110	*	91	16q11.2	44574019	44904017
AFP199200	CNS01DV7	BAC-R-1070N10	#	14		82330266	82541053
AFP229269	AL161670	BAC-R-804M7	*	14	14q21.3	46135365	46299284
AFP236718	AC010319	CTD-2521M24	*	61	19p13.3	4839920	5087628
AFP237679	60L69Z	*	*	4	4p16.3	4521455	4544888
AFP244615	*	*	AI494556;AW85055 3	3	3q13.12	116466893	116517043
AFP249599	AL157714	RP11-541H12	*.	1	1q22-23.3	161893354	162136704
AFP250422	AC012046	RP11-312P12	*	10	10q22.1	81289799	81650062
AFP262739	AC005884	hRPK.264_B_14	*	17	17q23.3	64245127	64365313
AFP275580	AC016773	*	*	3	3q21.3	141329005	141513510
AFP277451	AC055822	RP11-707M3	*	8	8q13.3	75395740	75583383
AFP279267	*	*	AI566086	01	10q11.1	52859924	52861338
AFP280451	AL133355	RP11-541N10	*	01	10q24.32	115276306	115467187
AFP290397	*	*	AA421069	15	15q15.3	48427462	48427830
AFP293220	AC012476	RP11-532F12	*	15	15p11.1	17263661	17480097
AFP297548	*	*	W52728	11	11911	57918740	57927327
AFP306591	AQ079258	2366B9	AW118928	9	6p22.3	19812023	19812791
AFP313600	AC005037	NH0469M07	*	2	2q33.1	205320800	205511307
AFP324816	AC011687	RP11-15120	*	2	2p21	49054619	49249783
AFP325761	AC012485	RP11-5024	*	2	2p24.3	17554756	17765537

AFP326051	AL132639	BAC-R-407N17	AI525611	14	14n111	10050403	20153358
AFP345861	AC015936	CTD-2534121	*	17	17921.2	44087441	44286594
AFP347179	AC025740	*	*	12	12q24.23	125918909	126134148
AFP372822	AL022240	3.28E+21	*	1	1912-21.2	138667522	138765140
AFP374312	*	*	AI253088	=	11923.3	128134250	128134589
AFP375952	*	*	AI741157	16	16p13.3	3479999	3500834
AFP395942	AC004235	*	*	16	16p13.3	4189155	4222465
AFP404202	*	*	AI133727	7		142961410	143641730
AFP404279	*	*	AI341602	4	4p16.3	1512179	1514256
AFP413680	AC006942	cosmid-R31181	*	19	19q13.33	59897688	59940397
AFP436666	*	*	AI814257	∞	8p21.3	18993217	19003942
AFP448623	*	*	AI140615	5	5q33.1	173540737	173547400
AFP460626	AC009131	RP11-502K10	#	91	16q22.1	70222075	7047.1703
AFP477303	AC008686	CTB-5E10	*	19	19p13.13	16491516	1.6677574
AFP501809	*	*	AW583171	9	6p21.1	50554924	50564907
AFP545268	AL138695	RP11-342J4	*	13	13q21.1	60450247	60714738
AFP561930	AL136221	RP11-391H12	*	13	13q34	108494503	108794286
AFP71288	*	*	AA493506	9	6q22.33	137477811	137478427
AFP74517	HS1056L3	RP5-1056L3	*	_	1p35.1-36.13	*	*
AFP93743	AC067942	RP11-791G16	*	4	4q21.22	77419530	77633569

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If a mammal has an insufficiency of a protein of interest (due to, for example, a mutated or absent gene), the corresponding wild-type gene can be introduced into the cells of the mammal. In one embodiment, a gene encoding a protein of interest is introduced into the animal using a viral vector. Such vectors include an attenuated or defective DNA virus, such as, but not limited to, herpes simplex virus (HSV), papillomavirus, Epstein Barr virus (EBV), adenovirus, adenoassociated virus (AAV), and the like. Defective viruses, which entirely or almost entirely lack viral genes, are preferred. A defective virus is not infective after introduction into a cell. Use of defective viral vectors allows for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Examples of particular vectors include, but are not limited to, a defective herpes simplex virus 1 (HSV1) vector (Kaplitt et al., Molec. Cell. Neurosci. 2;320-30, 1991); an attenuated adenovirus vector, such as the vector described by Stratford-Perricaudet et al. (J. Clin. Invest. 90:626-30, 1992); and a defective adeno-associated virus vector (Samulski et al., J. Virol. 61:3096-101, 1987; Samulski et al., J. Virol. 63:3822-28, 1989).

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Within another embodiment, a gene of interest is introducted into an animal by liposome-mediated transfection ("lipofection") essentially as disclosed above. Lipofection can be used to introduce exogenous genes into specific organs.

A gene of interest can also be introduced into an animal for gene therapy as a naked DNA plasmid using the methods disclosed above.

In another embodiment, polypeptide-toxin fusion proteins or antibody/fragment-toxin fusion proteins may be used for targeted cell or tissue inhibition or ablation, such as in cancer therapy. Of particular interest in this regard are conjugates of an AFP protein and a cytotoxin, which can be used to target the cytotoxin to a tumor or other tissue that is undergoing undesired angiogenesis or neovascularization.

In another embodiment, AFP-cytokine fusion proteins or antibody/fragment-cytokine fusion proteins may be used for enhancing *in vitro* cytotoxicity (for instance, that mediated by monoclonal antibodies against tumor targets) and for enhancing *in vivo* killing of target tissues (for example, blood and bone marrow cancers). See, generally, Hornick et al., *Blood* 89:4437-4447, 1997). In general, cytokines are toxic if administered systemically. The described fusion proteins enable targeting of a cytokine to a desired site of action, such as a cell having binding sites for an AFP protein, thereby providing an elevated local concentration of cytokine. Polypeptides, antibodies, or receptors target an undesirable cell or tissue

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(e.g., a tumor), and the fused cytokine mediates improved target cell lysis by effector cells. Suitable cytokines for this purpose include, for example, interleukin-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF).

In another embodiment, polypeptide-toxin fusion proteins or other binding partner-linked toxins may be used for targeted cell or tissue inhibition or ablation (for instance, to treat cancer cells or tissues). Target cells (i.e., those displaying a receptor for a polypeptide of interest) bind the polypeptide-toxin conjugate, which is then internalized, killing the cell. The effects of receptor-specific cell killing (target ablation) are revealed by changes in whole animal physiology or through histological examination. Thus, ligand-dependent, receptor-directed cyotoxicity can be used to enhance understanding of the physiological significance of a protein ligand. A preferred such toxin is saporin. Mammalian cells have no receptor for saporin, which is non-toxic when it remains extracellular. Alternatively, if the polypeptide of interest has multiple functional domains (i.e., an activation domain or a 15 ligand binding domain, plus a targeting domain), a fusion protein including only the targeting domain may be suitable for directing a detectable molecule, a cytotoxic molecule or a complementary molecule to a cell or tissue type of interest. In instances where the domain-only fusion protein includes a complementary molecule, the anticomplementary molecule can be conjugated to a detectable or cytotoxic molecule. Such domain-complementary molecule fusion proteins thus represent a generic targeting vehicle for cell- or tissue-specific delivery of generic anti-complementarydetectable/cytotoxic molecule conjugates.

The bioactive conjugates described herein can be intravenously, intraarterially or intraductally, or may be introduced locally at the intended site of action.

For pharmaceutical use, the proteins of the present invention are formulated according to conventional methods. Routes of delivery include topical, mucosal, and parenteral, the latter including intravenous and subcutaneous delivery. Intravenous administration will be by bolus injection or infusion over a typical period of one to several hours. In general, pharmaceutical formulations will include a protein of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water or the like. Formulations may further include one or more excipients, diluents, fillers, emulsifiers, preservatives, solubilizers, buffering agents, wetting agents, stabilizers, colorings, penetration enhancers, albumin to prevent protein loss on vial surfaces, etc. Topical formulations are typically provided as liquids, ointments, salves, gels, emulsions and the like. Methods of formulation are well known in the art and are disclosed, for example, in

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Remington: The Science and Practice of Pharmacy, Gennaro, ed., Mack Publishing Co., Easton, PA, 19th ed., 1995. Therapeutic doses will be determined by the clinician according to accepted standards, taking into account the nature and severity of the condition to be treated, patient traits, etc. Proteins of the present invention will generally be formulated to provide a dose of from 0.01 µg to 100 mg per kg patient weight per day, more commonly from 0.1 µg to 10 mg/kg/day, still more commonly from 0.1 µg to 1.0 mg/kg/day. Determination of dose is within the level of ordinary skill in the art. The proteins may be administered for acute treatment, over one week or less, often over a period of one to three days or may be used in chronic treatment, over several months or years. In general, a therapeutically effective amount is an amount sufficient to produce a clinically significant change in the targetted condition.

Within the laboratory research field, the proteins of the present invention can be used as molecular weight standards, or as standards in the analysis of cell phenotype, and as reagents for the study of cells, receptors, and other binding molecules. Such reagents will generally further comprise a second moiety, such as a label, binding partner, or toxin, that facilitates the detection of the protein when bound to its target. Many such systems are known in the art and are summarized above. Receptors and other cell-surface binding sites for proteins of the present invention can be identified by exposing a population of cells to a labelled protein under physiologic conditions, whereby the protein binds to the surface of the cell. Cells bearing receptors for a protein of interest can also be identified using the protein joined to a toxin, whereby receptor-bearing cells are killed by the toxin.

AFP proteins and antagonists thereof can be used as standards in assays of protein and protein inhibitors in both clinical and research settings. Such assays can comprise any of a number of standard formats, include radioreceptor assays and ELISAs. Protein standards can be prepared in labeled form using a radioisotope, enzyme, fluorophore, or other compound that produces a detectable signal. The proteins can be packaged in kit form, such kits comprising one or more vials containing the AFP protein and, optionally, a diluent, an antibody, a labeled binding protein, etc. Assay kits can be used in the research laboratory to detect protein and inhibitor activities produced by cultured cells or test animals.

Proteins of the present invention may also be used as protein and amino acid supplements, including hydrolysates. Specific uses in this regard include use as animal feed supplements and as cell culture components. Proteins rich in a particular amino acid can be used as a source of that amino acid.

Polynucleotides and polypeptides of the present invention will additionally find use as educational tools as a laboratory practicum kits for courses

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related to genetics and molecular biology, protein chemistry and antibody production Due to their unique polynucleotide and polypeptide sequences, and analysis. molecules of AFP protein or polynucleotide can be used as standards or as "unknowns" for testing purposes. For example, AFP polynucleotides can be used as aids in teaching students how to prepare expression constructs for bacterial, viral, and/or mammalian expression, including fusion constructs, wherein an AFP polynucleotide is the gene to be expressed; for determining the restriction endonuclease cleavage sites of the polynucleotides (which can be determined from the sequence using conventional computer software, such as MapDraw™ (DNASTAR, Madison, WI)); determining mRNA and DNA localization of AFP polynucleotides in tissues (e.g., by Northern and Southern blotting as well as polymerase chain reaction); and for identifying related polynucleotides and polypeptides by nucleic acid hybridization.

AFP polypeptides can be used educationally as aids to teach preparation of antibodies; identifying proteins by Western blotting; protein purification; 15 determining the weight of expressed AFP polypeptides as a ratio to total protein expressed; identifying peptide cleavage sites; coupling amino and carboxyl terminal tags; amino acid sequence analysis, as well as, but not limited to monitoring biological activities of both the native and tagged protein (i.e., receptor binding, signal transduction, proliferation, and differentiation) in vitro and in vivo. AFP polypeptides can also be used to teach analytical skills such as mass spectrometry, circular dichroism to determine conformation, in particular the locations of the disulfide bonds. x-ray crystallography to determine the three-dimensional structure in atomic detail, nuclear magnetic resonance spectroscopy to reveal the structure of proteins in solution. For example, a kit containing an AFP protein can be given to the student to analyze. Since the amino acid sequence would be known by the professor, the protein can be given to the student as a test to determine the skills or develop the skills of the student, the teacher would then know whether or not the student has correctly analyzed the polypeptide. Since every polypeptide is unique, the educational utility of zcub5 would be unique unto itself.

Antibodies that bind specifically to an AFP polypeptide can be used as a teaching aid to instruct students how to prepare affinity chromatography columns to purify the cognate polypeptide, cloning and sequencing the polynucleotide that encodes an antibody and thus as a practicum for teaching a student how to design humanized antibodies. The AFP polynucleotide, polypeptide or antibody would then be packaged by reagent companies and sold to universities so that the students gain skill in art of molecular biology. Because each polynucleotide and protein is unique, each polynucleotide and protein creates unique challenges and learning experiences for

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students in a lab practicum. Such educational kits containing an AFP polynucleotide, polypeptide or antibody are considered within the scope of the present invention.

The invention is further illustrated by the following non-limiting examples.

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EXAMPLES

Example 1

A protein of the present invention ("AFP") is produced in *E. coli* using a His₆ tag/maltose binding protein (MBP) double affinity fusion system as generally disclosed by Pryor and Leiting, *Prot. Expr. Pur.* 10:309-319, 1997. A thrombin cleavage site is placed at the junction between the affinity tag and AFP sequences.

The fusion construct is assembled in the vector pTAP98, which comprises sequences for replication and selection in *E. coli* and yeast, the *E. coli* tac promoter, and a unique Smal site just downstream of the MBP-His6-thrombin site coding sequences. The AFP cDNA is amplified by PCR using primers each comprising 40 bp of sequence homologous to vector sequence and 25 bp of sequence that anneals to the cDNA. The reaction is run using Taq DNA polymerase (Boehringer Mannheim, Indianapolis, IN) for 30 cycles of 94°C, 30 seconds; 60°C, 60 seconds; and 72°C, 60 seconds. One microgram of the resulting fragment is mixed with 100 ng of Smal-cut pTAP98, and the mixture is transformed into yeast to assemble the vector by homologous recombination (Oldenburg et al., *Nucl. Acids. Res.* 25:451-452, 1997). Ura⁺ transformants are selected.

Plasmid DNA is prepared from yeast transformants and transformed into *E. coli* MC1061. Pooled plasmid DNA is then prepared from the MC1061 transformants by the miniprep method after scraping an entire plate. Plasmid DNA is analyzed by restriction digestion.

E. coli strain BL21 is used for expression of AFP. Cells are transformed by electroporation and grown on minimal glucose plates containing casamino acids and ampicillin.

Protein expression is analyzed by gel electrophoresis. Cells are grown in liquid glucose media containing casamino acids and ampicillin. After one hour at 37°C, IPTG is added to a final concentration of 1mM, and the cells are grown for an additional 2-3 hours at 37°C. Cells are disrupted using glass beads, and extracts are prepared.

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Example 2

Larger scale cultures of AFP transformants are prepared by the method of Pryor and Leiting (ibid.). 100-ml cultures in minimal glucose media containing casamino acids and 100 µg/ml ampicillin are grown at 37°C in 500-ml baffled flasks to $OD_{600} \approx 0.5$. Cells are harvested by centrifugation and resuspended in 100 ml of the same media at room temperature. After 15 minutes, IPTG is added to 0.5 mM, and cultures are incubated at room temperature (ca. 22.5°C) for 16 to 20 hours with shaking at 125 rpm. The culture is harvested by centrifugation, and cell pellets are stored at -70°C.

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Example 3

For larger-scale protein preparation, 500-ml cultures of E. coli BL21 expressing the AFP-MBP-His6 fusion protein are prepared essentially as disclosed in Example 2. Cell pellets are resuspended in 100 ml of binding buffer (20 mM Tris, pH 7.58, 100 mM NaCl, 20 mM NaH₂PO₄, 0.4 mM 4-(2-Aminoethyl)-benzenesulfonyl fluoride hydrochloride [Pefabloc® SC; Boehringer-Mannheim], 2 µg/ml Leupeptin, 2 μg/ml Aprotinin). The cells are lysed in a French press at 30,000 psi, and the lysate is centrifuged at 18,000 x g for 45 minutes at 4°C to clarify it. Protein concentration is estimated by gel electrophoresis with a BSA standard.

Recombinant AFP fusion protein is purified from the lysate by affinity chromatography. Immobilized cobalt resin (Talon® resin; Clontech Laboratories, Inc., Palo Alto, CA) is equilibrated in binding buffer. One ml of packed resin per 50 mg protein is combined with the clarified supernatant in a tube, and the tube is capped and sealed, then placed on a rocker overnight at 4°C. The resin is then pelleted by centrifugation at 4°C and washed three times with binding buffer. Protein is eluted with binding buffer containing 0.2 M imidazole. The resin and elution buffer are mixed for at least one hour at 4°C, the resin is pelleted, and the supernatant is removed. An aliquot is analyzed by gel electrophoresis, and concentration is estimated. Amylose resin is equilibrated in amylose binding buffer (20 mM Tris-HCl, pH 7.0, 100 mM NaCl, 10 mM EDTA) and combined with the supernatant from the Talon resin at a ratio of 2 mg fusion protein per ml of resin. Binding and washing steps are carried out as disclosed above. Protein is eluted with amylose binding buffer containing 10 mM maltose using as small a volume as possible to minimize the need for subsequent concentration. The eluted protein is analyzed by gel electrophoresis and staining with Coomassie blue using a BSA standard, and by Western blotting using an anti-MBP antibody.

Example 4

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An expression plasmid containing all or part of a polynucleotide encoding AFP is constructed via homologous recombination. An AFP coding sequence comprising the ORF with 5' and 3' ends corresponding to the vector sequences flanking the insertion point is prepared by PCR. The primers for PCR each include from 5' to 3' end: 40 bp of flanking sequence from the vector and 17 bp corresponding to the amino or carboxyl termini from the open reading frame of AFP.

Ten µl of the 100 µl PCR reaction mixture is run on a 0.8% lowmelting-temperature agarose (SeaPlaque GTG®; FMC BioProducts, Rockland, ME) gel with 1 x TBE buffer for analysis. The remaining 90 ul of the reaction mixture is precipitated with the addition of 5 µl 1 M NaCl and 250 µl of absolute ethanol. The plasmid pZMP6, which has been cut with Smal, is used for recombination with the PCR fragment. Plamid pZMP6 is a mammalian expression vector containing an expression cassette having the cytomegalovirus immediate early promoter, multiple restriction sites for insertion of coding sequences, a stop codon, and a human growth hormone terminator; an E. coli origin of replication; a mammalian selectable marker expression unit comprising an SV40 promoter, enhancer and origin of replication, a DHFR gene, and the SV40 terminator; and URA3 and CEN-ARS sequences required for selection and replication in S. cerevisiae. It was constructed from pZP9 (deposited at the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, under Accession No. 98668) with the yeast genetic elements taken from pRS316 (available from the American Type Culture Collection, 10801 University Boulevard, Manassas, VA, under Accession No. 77145), an internal ribosome entry site (IRES) element from poliovirus, and the extracellular domain of CD8 truncated at the C-terminal end of the transmembrane domain.

One hundred microliters of competent yeast (S. cerevisiae) cells are independently combined with 10 μl of the various DNA mixtures from above and transferred to a 0.2-cm electroporation cuvette. The yeast/DNA mixtures are electropulsed using power supply (BioRad Laboratories, Hercules, CA) settings of 0.75 kV (5 kV/cm), ∞ ohms, 25 μF. To each cuvette is added 600 μl of 1.2 M sorbitol, and the yeast is plated in two 300-μl aliquots onto two URA-D plates (1.8% agar in 2% D-glucose, 0.67% yeast nitrogen base without amino acids, 0.056% -Ura -Trp -Thr powder [made by combining 4.0 g L-adenine, 3.0 g L-arginine, 5.0 g L-aspartic acid, 2.0 g L-histidine, 6.0 g L-isoleucine, 8.0 g L-leucine, 4.0 g L-lysine, 2.0 g L-methionine, 6.0 g L-phenylalanine, 5.0 g L-serine, 5.0 g L-tyrosine, and 6.0 g L-valine], and 0.5% 200X tryptophan, threonine solution [3.0% L-threonine, 0.8% L-tryptophan in H₂O]) and incubated at 30°C. After about 48 hours, the Ura⁺ yeast

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transformants from a single plate are resuspended in 1 ml H_2O and spun briefly to pellet the yeast cells. The cell pellet is resuspended in 1 ml of lysis buffer (2% Triton X-100, 1% SDS, 100 mM NaCl, 10 mM Tris, pH 8.0, 1 mM EDTA). Five hundred microliters of the lysis mixture is added to an Eppendorf tube containing 300 μ l acidwashed glass beads and 200 μ l phenol-chloroform, vortexed for 1 minute intervals two or three times, and spun for 5 minutes in an Eppendorf centrifuge at maximum speed. Three hundred microliters of the aqueous phase is transferred to a fresh tube, and the DNA is precipitated with 600 μ l ethanol (EtOH), followed by centrifugation for 10 minutes at 4°C. The DNA pellet is resuspended in 10 μ l H_2O .

Transformation of electrocompetent *E. coli* host cells (Electromax DH10BTM cells; obtained from Life Technologies, Inc., Gaithersburg, MD) is done with 0.5-2 ml yeast DNA prep and 40 μl of cells. The cells are electropulsed at 1.7 kV, 25 μF, and 400 ohms. Following electroporation, 1 ml SOC (2% BactoTM Tryptone (Difco, Detroit, MI), 0.5% yeast extract (Difco), 10 mM NaCl, 2.5 mM KCl, 10 mM MgCl₂, 10 mM MgSO₄, 20 mM glucose) is plated in 250-μl aliquots on four LB AMP plates (LB broth (Lennox), 1.8% BactoTM Agar (Difco), 100 mg/L Ampicillin).

Individual clones harboring the correct expression construct for AFP are identified by restriction digest to verify the presence of the AFP insert and to confirm that the various DNA sequences have been joined correctly to one another. The inserts of positive clones are subjected to sequence analysis. Larger scale plasmid DNA is isolated using a commercially available kit (QIAGEN Plasmid Maxi Kit, Qiagen, Valencia, CA) according to manufacturer's instructions. The correct construct is designated pZMP6/AFP.

Recombinant protein is produced in BHK cells transfected with pZMP6/AFP. BHK 570 cells (ATCC CRL-10314) are plated in 10-cm tissue culture dishes and allowed to grow to approximately 50 to 70% confluence overnight at 37°C, 5% CO₂, in DMEM/FBS media (DMEM, Gibco/BRL High Glucose; Life Technologies), 5% fetal bovine serum (Hyclone, Logan, UT), 1 mM L-glutamine (JRH Biosciences, Lenexa, KS), 1 mM sodium pyruvate (Life Technologies). The cells are then transfected with pZMP6/AFP by liposome-mediated transfection using a 3:1 (w/w) liposome formulation of the polycationic lipid 2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propaniminium-trifluoroacetate and the neutral lipid dioleoyl phosphatidylethanolamine in membrane-filtered water (LipofectamineTM Reagent; Life Technologies, Garithersburg, MD), in serum free (SF) media (DMEM supplemented with 10 mg/ml transferrin, 5 mg/ml insulin, 2 mg/ml fetuin, 1% L-glutamine and 1% sodium pyruvate). The plasmid is diluted into 15-ml tubes to a total final volume of 640 μl with SF media. 35 μl of the lipid mixture is

mixed with 605 μl of SF medium, and the resulting mixture is allowed to incubate approximately 30 minutes at room temperature. Five milliliters of SF media is then added to the DNA:lipid mixture. The cells are rinsed once with 5 ml of SF media, aspirated, and the DNA:lipid mixture is added. The cells are incubated at 37°C for five hours, then 6.4 ml of DMEM/10% FBS, 1% PSN media is added to each plate. The plates are incubated at 37°C overnight, and the DNA:lipid mixture is replaced with fresh 5% FBS/DMEM media the next day. On day 5 post-transfection, the cells are split into T-162 flasks in selection medium (DMEM + 5% FBS, 1% L-Gin, 1% NaPyr, 1 μM methotrexate). Approximately 10 days post-transfection, two 150-mm culture dishes of methotrexate-resistant colonies from each transfection are trypsinized, and the cells are pooled and plated into a T-162 flask and transferred to large-scale culture.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

We claim:

- 1. An isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422.
- 2. The isolated polypeptide of claim 1 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 3. The isolated polypeptide of claim 1 or claim 2 which is from 15 to 2235 amino acid residues in length.
- 4. The isolated polypeptide of claim 3 which is operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423.
- 5. The isolated polypeptide of any of claims 1-4 comprising at least 30 contiguous residues of SEQ ID NO:M.
- 6. The isolated polypeptide of any of claims 1-5 comprising at least 47 contiguous residues of SEQ ID NO:M.
- 7. An isolated, mature protein encoded by a sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421.
- 8. The protein of claim 7 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 9. An isolated polynucleotide comprising a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer from 1 to 421.

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- 10. The isolated polynucleotide of claim 9 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 11. An expression vector comprising the following operably linked elements:
 - a transcription promoter;
- a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and
 - a transcription terminator.
- 12. The expression vector of claim 11 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 13. A cultured cell comprising the expression vector of claim 11 or claim 12.
- 14. A method of producing a polypeptide comprising culturing the cell of claim 13 under conditions whereby said sequence of nucleotides is expressed, and recovering said polypeptide.
 - 15. A polypeptide produced by the method of claim 14.
- 16. An isolated polynucleotide encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide.
- 17. An expression vector comprising the following operably linked elements:

- a transcription promoter;
- a DNA segment encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide; and a transcription terminator.
- 18. A cultured cell comprising the expression vector of claim 17, wherein the cell expresses the DNA segment and produces the encoded fusion protein.
- 19. A method of producing a protein comprising culturing the cell of claim 18 under conditions whereby said DNA segment is expressed, and recovering said second polypeptide.
- 20. An antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer from 2 to 422.

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SEQUENCE LISTING

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					ccc Pro											192
					atc Ile 70											240

				-							cta Leu		_	Ile		288
											acg Thr					336
											cat His 125			_		384
					•						gct Ala			-		432
											ttt Phe					480
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Gln	Arg	Asn 195	Val	Ala	Ser	Leu	Ala 200	Trp	Lys	Pro	Leu	Ser 205	Ala	Ser	Val
Leu	Ala 210	Val	Ala	Cys	Gln	Ser 215	Cys	Пe	Leu	Ile	Trp 220	Thr	Leu	Asp	Pro
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Thr 305	Thr	Pro	Ser	Ala	Val 310	Phe	Arg	Val	Trp	G1u 315	Ala	Gln	Met	Trp	Thr 320
Cys	Glu	Arg	Trp	Pro 325	Thr	Leu	Ser	Gly	Arg 330	Cys	Gln	Thr	Gly	Cys 335	Trp
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465					470				•	475					480		
	He			485					490					495		٠	
	Leu		500					505				-	510				
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145 Gln	Ph△	Glv	Val	Ala	150 Val	Leu	Δcn	Acn	Lve	155	Tvr	اد٧	اد\ <i>ا</i>	Glv	160 Glv		
uiii	· HC	uiy	¥ CI I	165	¥ a i	Leu	ν∍h	vsh	170	Leu	ועו	vai	vai	175	ary		
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						tcg Ser										768
		-				gca Ala										816
						gat Asp		_	_	_	-		_	_		864
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						gat Asp		-	-		_			_	-	960
						gag Glu										1008
		Phe				ctg Leu	Gly									1056
-	Thr	-		-		cag Gln						-	_		•	1104

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		ccc Pro									1440
		gct Ala									1488
		999 Gly 500		Thr							1536
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PCT/US00/29052

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15

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Leu	Arg	Leu 515	Glu	Pro	Asn	Ala	G1n 520	Ala	G1n	Met	Tyr	Arg 525	Leu	Thr	Leu
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17

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Пe	Ser	Thr 195	Met	Arg	Pro	Leu.	A1a 200	Thr	Ala	Tyr	Lys	Ala 205	Ser	Thr	Ser	
Asp	Tyr 210	Gln	Val	Ile	Ser	Asp 215	Arg	Gln	Thr	Pro	Lys 220	Lys	Asp	Glu	Ser	
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His	Arg 50	Thr	His	۷a٦	Val	A1 a 55	Arg	Lys	Met	Tyr	Lys 60	Ile	Leu	Asp	Leu		
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												cgg Ara				9	6

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			gtt Val													4	80
			aga Arg													. 5	28
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Ser Val Ala Asp Thr Leu Gly Thr Ala His Ser Pro Lys Asp Gly Ser 50 55 60

Ser Val His Ser Thr Thr Ala Ser Ala Arg Arg Asn Ser Ser Ser Pro 70 75 80

Val Ser Pro Ala Ser Val Pro Gly Gln Arg Arg Leu Ala Ser Arg Asn 85 90 95

Gly Asp Leu Asn Leu Gln Val Ala Pro Pro Pro Pro Ser Ala His Pro 100 105 110

Gly Met Asp Gln Val His Pro Gln Asn Ile Pro Asp Ser Pro Met Ala 115 120 125

Asn Ser Gly Pro Leu Cys Cys Thr Ile Cys His Glu Arg Leu Glu Asp 130 135 140

Thr His Phe Val Gln Cys Pro Ser Val Pro Ser His Lys Phe Cys Phe 145 150 155 160

Pro Cys Ser Arg Glu Ser Ile Lys Ala Gln Gly Ala Thr Gly Glu Val 165 170 175

Tyr Cys Pro Ser Gly Glu Lys Cys Pro Leu Val Gly Ser Asn Val Pro 180 185 190

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Lys Val Lys Lys Glu Arg Asp Pro 210 215

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PCT/US00/29052

WO 01/29221

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48

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Val Ser Phe Gln Gly Phe Ile Leu Gln Val Gly Ser Gly Ala Ala Ala
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                                            60
Glu Pro Ser Arg Gly Thr Gly Ser Ser Gly Pro Ser Ser Gln His Pro
65
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Leu Ser Gln Ala His Arg Gln Gly Asn Phe Val Asp Ile Val Asp Ala
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Val His Ser Ser Arg Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu
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			Val										Ala		ttc Phe	144
		Ala										Trp			ttc Phe	192
									ata Ile							240
									aag Lys 90							288
									tac Tyr							336
aag Lys	agc Ser	tat Tyr 115	gag G1u	acc Thr	atg Met	atg Met	agg Arg 120	gtg Val	ggc Gly	aag Lys	agg Arg	ggc Gly 125	ctg Leu	aac Asn	ctt Leu	384
									gcc Ala							432
									cag Gln							480
									cct Pro 170							528
									gag Glu							576

26

•

			180					185					190				
	ctg Leu		Leu													,	624
	tct Ser 210												_				672
	aaa Lys																720
	cgg Arg			-	-						-		•	tga *			765
	<2 <2				oiens	5											
Met 1	</td <td>100> Ser</td> <td></td> <td>Ile 5</td> <td>Ile</td> <td>Ser</td> <td>Arg</td> <td>Ļeu</td> <td>Val</td> <td>Val</td> <td>Leu</td> <td>Ile</td> <td>Phe</td> <td>-</td> <td>Thr</td> <td></td> <td></td>	100> Ser		Ile 5	Ile	Ser	Arg	Ļeu	Val	Val	Leu	Ile	Phe	-	Thr		
	Tyr	Pro	Ala 20		Ser	Ser	Tyr	Lys 25		Val	Lys	Thr	Lys 30	15 Asn	Val		
Lys	Glu	Tyr 35	Val	Lys	Trp	Met	Met 40	Tyr	Trp	Пe	Val	Phe 45	Ala	Phe	Phe		
Thr	Thr 50	Ala	Glu	Thr	Leu	Thr 55	Asp	Ile	Val	Leu	Ser 60	Trp	Phe	Pro	Phe		
Tyr 65	Phe	Glu	Leu	Lys	Ile 70	Ala	Phe	Val	Пе	Trp 75	Leu	Leu	Ser	Pro	Tyr 80		
Thr	Lys	Gly	Ser	Ser 85	Val	Leu	Tyr	Arg	Lys 90	Phe	Val	His	Pro	Thr 95	Leu		
Ser	Asn	Lys	Glu 100	Lys	Glu	Ile	Asp	G1u 105		Пе	Thr	Gln	Ala 110		Asp		
Lys	Ser	Tyr 115	Glu	Thr	Met	Met	Arg 120		Gly	Lys	Arg	Gly 125		Asn	Leu		
41a	Ala 130		Ala	Ala	Val	Thr 135		Ala	Ala	Lys	Gly 140		Gly	Val	Leu		-
Ser	Glu	Lys	Leu	Arg	Ser		Ser	Met	Gln	Asp		Thr	Leu	He	Ara		

145 150 155 160 Asp Glu Asp Ala Leu Pro Leu Gln Arg Pro Asp Gly Arg Leu Arg Pro 170 Ser Pro Gly Ser Leu Leu Asp Thr Ile Glu Asp Leu Gly Asp Asp Pro 180 185 190 Ala Leu Ser Leu Arg Ser Ser Thr Asn Pro Ala Asp Ser Arg Thr Glu 200 205 Ala Ser Glu Asp Asp Met Gly Asp Lys Ala Pro Lys Arg Ala Lys Pro 215 220 Ile Lys Lys Ala Pro Lys Ala Glu Pro Leu Ala Ser Lys Thr Leu Lys 230 235 240 Thr Arg Pro Lys Lys Thr Ser Gly Gly Gly Asp Ser Ala 245 250 <210> 17 <211> 408 <212> DNA <213> Homo sapiens .<220> <221> CDS <222> (1)...(408) <221> misc feature <222> (1)...(408) <223> n = A.T.C or G<400> 17 atg gcc cat agg ggc gtg tca gct gtg gtc gtg gga gct gac cgc gtg 48 Met Ala His Arg Gly Val Ser Ala Val Val Gly Ala Asp Arg Val 1 10 gtt gcc aac ggn gac aca gcc aac aag gtg ggc acc tac cag ctg gcc 96 Val Ala Asn Xaa Asp Thr Ala Asn Lys Val Gly Thr Tyr Gln Leu Ala 20 25 30 att gtc gcc aag cac cat ggc att ccc ttc tac gtg gct gcc ccc agc 144 Ile Val Ala Lys His His Gly Ile Pro Phe Tyr Val Ala Ala Pro Ser 35 40 tct tca tgt gac ctc cgt ctg gag acc ggc aag gag atc att att gaa 192 Ser Ser Cys Asp Leu Arg Leu Glu Thr Gly Lys Glu Ile Ile Ile Glu 50 55 60

	cga Arg														-	240
	cct Pro															288
_	ctc Leu											-		_		336
	gag Glu															384
	cta Leu 130						taa *									408
	<'a	210> 211> 212> 213>	135 PRT	sar	oiens	5										
	<'a	222>	VAR] (1). Xaa	(1		nino	Acid	d								
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Met 1	Ala			G1y 5	Val	Ser	Ala	Val	Val 10	Val	Gly	Ala	Asp	Arg 15	Val	
Val	Ala	Asn	Xaa 20	Asp	Thr	Ala	Asn	Lys 25	Val	Gly	Thr	Tyr	G1n 30	Leu	Ala	
IJе	Val	Ala 35		His	His	Gly	Ile 40		Phe	Tyr	Val	A1a 45		Pro	Ser	
Ser	Ser 50		Asp	Leu	Arg	Leu 55		Thr	Gly	Lys	Glu 60		He	Ile	Glu	
Glu 65	Aṛg	Pro	Gly	Gln	G1u 70		Thr	Asp	Val	Asn 75		Val	Arg	Ile	Ala 80	
	Pro	Gly	Пе	G1 <i>y</i> 85	Val	Trp	Asn	Pro	A1a 90		Asp	Val	Thr	Pro 95		

Asp	Leu	Ile	Thr 100	Gly	Gly	Пe	Ile	Thr 105	Glu	Leu	Gly	Val	Phe 110	Ala	Pro	
Glu	Glu	Leu 115	Arg	Thr	Ala	Leu	Thr 120	Thr	Thr	Пe	Ser	Ser 125		Asp	Gly	
Thr	Leu 130	Asp	Gly	Pro	Gln	Met 135										
-		210> 211> 212> 213>	828 Dna	o sap	oiens	5										
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		100>														
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					-		_	_		ctg Leu	_			-		96
_					_					aaa Lys,					_	144
_	_		_						-	ggc Gly	_	-				192
										ccc Pro 75						240
										ctg Leu						288
							-	_		gtg Val		-				336

			agt Ser										_	_		384	1
			ttt Phe			-										432	?
			ctg Leu						_	_	-	-	_	-	_	480)
	-		ggc Gly		-	-						-				528	}
		-	gag Glu 180		_			_			-		_		_	576	;)
			cag Gln													624	ŀ
A1a			ctg Leu							_					-	672	•
	-		cat His	Tyr	-	_			-		_		_			720	
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_			_		999 Gly		_							-		4	32
	-		-		gaa Glu 150		_								_	4	80
	-		-	-	caa Gln	-				-	_				-	5.	28
					gaa G1u											5	76
		_	_		ttc Phe			Gly			-					6	24
-	-				cca Pro				_				_	_	_	6	72
			_		gag G1u 230	_		_			-					7:	20
					ggt Gly											7(68 ⁻
					atc Ile											8	16
			-		cag Gln		_	-								80	64
tac	aaa	tgt	gag	gtc	tgc	agc	aag	gcc	ttc	tcc	cag	agc	tct	gac	ctc	9	12

Tyr	Lys 290		Glu	Val	Cys	Ser 295	Lys	Ala	Phe	Ser	Gln 300	Ser	Ser	Asp	Leu	
	Lys								gag Glu							960
									tct Ser 330							1008
									aag Lys	-			_		_	1056
								_	cga Arg		-	-			_	1104
					-	_			tgc Cys		•	_		_	_	1152
									gtg Val							1200
							_	_	ttc Phe 410		-		-	-		1248
									gag Glu							1296
									tcg Ser		_	_				1344
					Gly				agc Ser	-		_			_	1392
acc	ttc	aat	cgc	tcc	tcc	act	ctc	atc	cag	cac	cag	cgc	tcc	cac	acg	1440

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tcc tcc acg ctt ctg cag cat cac cgg gtc cac agt ggc gag cgg cct Ser Ser Thr Leu Leu Gln His His Arg Val His Ser Gly Glu Arg Pro 500 505 510	1536
tac aag tgc gat gac tgc gga aag gcc ttc tcc cag agc tcc gac ctc Tyr Lys Cys Asp Asp Cys Gly Lys Ala Phe Ser Gln Ser Ser Asp Leu 515 520 525	1584
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G1u 145	Ser	Ser	Arg	Tyr	Glu 150	Ser	Gln	Asn	Thr	G1u 155	Leu	Lys	Thr	Gln	Ser 160
Pro	Glu	Phe	Glu	Ala 165	Gln	Ser	Ser	Lys	Phe 170	Gln	Glu	Gly	Ala	G1u 175	Met
	Leu		180			-		185					190	•	
	Pro	195	·				200	-				205			·
·	Leu 210			_		215					220	_			
225	Thr				230					235		_			240
	Leu	_		245	-	_		-	250			_	-	255	
	Pro	_	260					265			-		270	_	
	Ser	275					280					285			
	Lys 290	-			-	295			1		300			,	
305	Lys			_	310			-		315					320
	Cys			325			-		330	_				335	
	Thr		340					345	-	-			350		_
	Phe	355	·			-	360		-			365			
His	G1u 370	Arg	Pro	Tyr	Ser	Cys 375	Thr	Glu	Cys	Gly	Lys 380	Cys	Tyr	Ser	Gln
Asn 385	Ser	Ser	Leu	Arg	Ser 390	His	Gln	Arg	Val	His 395	Thr	Gly	Gln	Arg	Pro 400
Phe	Ser	Cys		Ile 405	Cys	Gly	Lys	Ser	Phe 410	Ser	Gln	Arg	Ser	Ala 415	Leu
Пe	Pro	His	Ala 420	Arg	Ser	His	Ala	Arg 425	Glu	Lys	Pro	Phe	Lys 430	Cys	Pro
Glu	Cys	Gly 435	Lys	Arg	Phe	Gly	G1n 440	Ser	Ser	Val	Leu	A1a 445	Пe	His	Ala
Ara	Thr	His	Leu	Pro	Glv	Ara	Thr	Tvr	Ser	Cvs	Pro	Asn	Cvs	Glv	Ιvς

	450					455					460					
Thr 465	Phe	Asn	Arg	Ser	Ser 470	Thr	Leu	Ile	Gln	His 475	Gln	Arg	Ser	His	Thr 480	
Gly	Glu	Arg	Pro	Tyr 485	Arg	Cys	Ala	Val	Cys 490	Gly	Lys	Gly	Phe	Cys 495	Arg	
Ser	Ser	Thr	Leu 500	Leu	Gln	His	His	Arg 505	Val	His	Ser	Gly	G1u 510	Arg	Pro	
Tyr	Lys	Cys 515	Asp	Asp	Cys	Gly	Lys 520	Ala	Phe	Ser	Gln	Ser 525	Ser	Asp	Leu	
Пe	Arg 530	His	Gln	Arg	Thr	His 535	Ala	Ala	Gly	Arg	Arg 540					
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_		_		_	-	atc Ile	_	_	-					_	_	144
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_	_		•			gag Glu	•	•			-	_	_	-		240
_	_		_			cac His			-				-	-		288

38

85 90 95 aga atc atc acc acg gcg gtg gac aag cgg gtc aat gac ctt ttc cgc 336 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100 105 110 atc atc cca ggc att ggg aac ttt ggc gac cgc tac ttt ggg aca gac 384 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp 120 115 125 gcg gtc ccc gat ggc agt gac gag gag gaa gtg gcc tac acg ggt tag 432 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly * 130 135 <210> 24 <211> 143 <212> PRT <213> Homo sapiens <400> 24 Met Glu Pro Ala Leu Arg Ala Val Cys Lys Asp Val Arg Ile Gly Thr Ile Leu Ile Gln Thr Asn Gln Leu Thr Gly Glu Pro Glu Leu His Tyr 25 Leu Arg Leu Pro Lys Asp Ile Ser Asp Asp His Val Ile Leu Met Asp 40 45 Cys Thr Val Ser Thr Gly Ala Ala Ala Met Met Ala Val Arg Val Leu 55 60 Leu Asp His Asp Val Pro Glu Asp Lys Ile Phe Leu Leu Ser Leu Leu 75 70 Met Ala Glu Met Gly Val His Ser Val Ala Tyr Ala Phe Pro Arg Val 90 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 105 100 110 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp 120 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly 130 135 140 <210> 25

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WO 01/29221

PCT/US00/29052

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40

145					150			155			160		
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		_	gga Gly 180	-				-	_		_	Ę	576
-		_	gag Glu			_					_	(524
			999 Gly							_		6	572
			atc Ile									7	720
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			ggc G1y 260									8	816
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<213> Homo sapiens

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				ttg Leu		_	_			_	_		192
				atc Ile 70									240
				gaa Glu									288
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				cgc Arg		-		-	-	-	 _	-	384
				gaa Glu									432

	130					135					140					
-			_		cct Pro 150	_		-	_	-			-			480
-	-		-		act Thr					-	-	_	-	_	-	528
					aca Thr				-							576
		-	_	-	gct Ala					_			-		-	624
-				-	act Thr											672
-		-		_	aca Thr 230	-		_		_	-	_				720
-			-		gaa Glu		-	-			-	-	_			768
		-			ctt Leu											795
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Arg	Arg	Ile	Ile 20	Gly	Leu	Lys	Asp	G1u 25	Phe	Tyr	Asn	Arg	Tyr 30	Ile	Thr
Lys	Gly	Asn 35	Leu	Phe	Glu	Pro	Va1 40	Ile	Asn	Ala	Leu	Leu 45	Asp	Asn	Gly
Thr	Arg 50	Tyr	Asn	Leu	Leu	Asn 55	Ser	Ala	Val	Ile	Glu 60	Leu	Phe	Glu	Phe
65					70					75			Val		80
				85					90				Phe	95	·
Leu	Lys	Thr	Lys 100	Tyr	Glu	Gln	Lys	Lys 105	Asn	Ser	Val	Pro	Ser 110	Ile	Leu
Arg	Ser	Asn 115	Arg	Phe	Arg	Arg	Asp 120	Ala	Lys	Ala	Leu	Glu 125	Glu	Asp	Glu
Glu	Met 130	Trp	Phe	Asn	Glu	Asp 135	G1u	Glu	Glu	Glu	Gly 140	Lys	Ala	Val	Val
A1a 145	Pro	Val	Glu	Lys	Pro 150	Lys	Pro	Glu	Asp	Asp 155	Phe	Pro	Asp	Asn	Tyr 160
Glu	Lys	Phe	Met	G1u 165	Thr	Lys	Lys	Ala	Lys 170	Glu	Ser	Glu	Asp	Lys 175	Glu
			180					185	_		-		Thr 190		
His	Ser	Ala 195	Ser	Ala	Ala	Asn	G1y 200	Thr	Asn	Ser	Lys	Ser 205	Val	Val	Ala
	210					215					220	_	Thr		
225					230					235			Gly		240
Asp	Tyr	Pro	Asp	Asp 245	Glu	Glu	Glu	Asp	G1u 250	Glu	Glu	Xaa	Ser	Ser 255	Pro
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<213> Homo sapiens

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						gat Asp 55										192
						gag G1u									-	240
-	-	-			_	ggt Gly			-	_			-			288
						ggt Gly										336
				_	_	att Ile				-			-			384
						gaa Glu 135						-				432
						gtc Val					_			-		480
cag	ctg	gct	gga	ctg	aca	ttg	ttg	aca	aac	atg	act	gtt	acc	aat	gac	528

Gln	Leu	Ala	Gly	Leu 165	Thr	Leu	Leu	Thr	Asn 170	Met	Thr	Val	Thr	Asn 175	Asp	
	cag Gln								Thr							576
	act Thr					_	_			_	_		-			624
	ttg Leu 210	Ser														672
_	gat Asp							-		-	-	tag *				711
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	Ala		20					25					30	_	-	
	Gly	35					40					45			·	
	Thr 50					55					60					•
.ys 55	Leu	Leu	Tyr	Leu	Leu 70	Glu	Ser	Thr	Glu	Asp 75	Pro	Val	Пe	Ile	Glu 80	
ırg	Ala	Leu	Ile	Thr 85	Leu	Gly	Asn	Asn	A1a 90	Ala	Phe	Ser	Val	Asn 95	G1n	
la	Пe	Пe	Arg 100	G1u	Leu	Gly	Gly	Ile 105	Pro	Пе	Val	Ala	Asn 110	Lys	Ile	
sn	His	Ser 115	Asn	G1n	Ser	Ile	Lys 120	Glu	Lys	Ala [,]	Leu	Asn 125	Ala	Leu	Asn	
sn	Leu 130	Ser	Val	Asn	Val	Glu 135	Asn	Gln	Ile	Lys	Ile 140	Lys	Ile	Tyr	Ile	

Ser 145	Gln	Val	Cys	Glu	Asp 150	Val	Phe	Ser	Gly	Pro 155	Leu	Asn	Ser	Ala	Val 160	
G1n	Leu	Ala	Gly	Leu 165		Leu	Leu	Thr	Asn 170		Thr	Val	Thr	Asn 175	Asp	
His	Gln	His	Met 180	Leu	His	Ser	Tyr	Ile 185	Thr	Asp	Leu	Phe	Gln 190	Val	Leu	
Leu	Thr	Gly 195		Gly	Asn	Thr	Lys 200	Val	Gln	Val	Leu	Lys 205	Leu	Leu	Leu	
Asn	Leu 210	Ser	Glu	Asn	Pro	Ala 215	Met	Thr	Glu	Gly	Leu 220	Leu	Arg	Ala	Gln	
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	ccg Pro															96
	gtc Val		Ala		Leu	Ala	Arg	Asn	Ala	Glu	His					144
	ctg Leu 50															192
	tgg Trp															240
cag	gag	tgg	ctg	gcg	gct	gtg	ggc	gat	gac	tat	gct	gct	gtg	gtc	tgg	288

Gln	Glu	Trp	Leu	A1a 85	Ala	Val	Gly	Asp	Asp 90	Tyr	Ala	Ala	Val	Va1 95	Trp		
				gag Glu												33	6
				gaa Glu				Phe					_	_	-	38	4
				gcc Ala									-		-	43	2
				att Ile	-				_		-				_	48	0
				cca Pro 165		-	_		_	-	-		_			528	3
				tgg Trp												576	5
				ttc Phe												624	1
		Pro		gtc Val		Ser	Thr	Phe		Ala						672	2
				ctt Leu	-			-								720)
			Asp	atc Ile 245												768	3
gtc	tcc	gtc	cac	gtg	tgc	aat	gag	cac	cgt	tat	9 99	tac	atg	aat	gtg	816	5

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Val	Ser	Val	His 260	Val	Cys	Asn	G1u	His 265	Arg	Tyr	Gly	Tyr	Met 270	Asn	Val	
			tcc Ser													864
			tta Leu								-	_	_	-		912
			act Thr													960
			gtc Val													1008
			tcg Ser 340													1056
			ggc Gly													1104
			ctc Leu													1152
			gag Glu	Val		-			-						-	1200
			gcc Ala													1248
			gag Glu 420				Arg					Arg				1296
gat	gtg	gag	gca	gag	aaa	ctg	tct	tgg	gac	ctg	atc	tac	ctc	gga	cgg	1344

Asp	Val	G1u 435	Ala	Glu	ı Lys	Leu	Ser 440		Asp	Leu	Пe	Tyr 445		ı Gly	Arg	
aag Lys	cag Gln 450	Val	aac Asn	cct Pro	gag G1u	aag Lys 455	gag Glu	acg Thr	gcc Ala	gtg Val	gag Glu 460	Gly	ctg Leu	ccg Pro	ggc Gly	1392
ctg Leu 465	Val	gtg Val	gct Ala	999 Gly	tac Tyr 470	tcc Ser	tac Tyr	tgg Trp	acg Thr	ctg Leu 475	gcc Ala	tat Tyr	gcc Ala	ctg Leu	cgt Arg 480	1440
ctg Leu	gcg Ala	ggt Gly	gcc Ala	cgc Arg 485	aag Lys	ctg Leu	ctg Leu	gcc Ala	tca Ser 490	cag Gln	cct Pro	ctg Leu	cgc Arg	cgc Arg 495	atg Met	1488
ctg Leu	ccc Pro	gtg Val	gac Asp 500	gag Glu	ttc Phe	ctg Leu	ccc Pro	atc Ile 505	atg Met	ttc Phe	gac Asp	cag Gln	cac His 510	ccc Pro	aac Asn	1536
gag Glu	cag Gìn	tac Tyr 515	aag Lys	gca Ala	cac His	ttc Phe	tgg Trp 520	cca Pro	cgg Arg	gac Asp	ctg Leu	gtg Val 525	gcc Ala	ttc Phe	tcc Ser	1584
gcc Ala	cag Gln 530	ccc Pro	ctg Leu	ctc Leu	gct Alä	gcc Ala 535	cct Pro	acc Thr	cac His	Tyr	gcc Ala 540	999 Gly	gac Asp	gcc Ala	gag Glu	1632
tgg Trp 545	ctc Leu	agt Ser	gac Asp	Thr	gag Glu 550	aca Thr	tcc Ser	tct Ser	Pro	tgg Trp 555	gat Asp	gat Asp	gac Asp	agc Ser	ggc Gly 560	1680
cgc Arg	ctc Leu	atc Ile	Ser	tgg Trp 565	agc Ser	ggc Gly:	tcc Ser	Gln	aag Lys 570	acc Thr	ctg Leu	cgc Arg	Ser	ccc Pro 575	gcc Ala	1728
tgg Trp		tga *														1737

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	Pro	Trp	Leu 20	•	Ala	Ala	Gly	Va1 25		Glu	Ser	Pro			Al
۷a۱	Val			Ile	Leu	Ala			Ala	Glu	His		30 Leu	Pro	His
Tyr	Leu 50	35 G1y	Ala	Leu	Glu		40 Leu	Asp	Tyr	Pro	_	45 Ala	Arg	Met	Ala
Leu 65		Cys	Ala	Thr	Asp 70	55 His	Asn	Val	Asp	Asn 75	60 Thr	Thr	Glu	Met	Lei 80
	Glu	Trp	Leu	A1 a 85	Ala	Val	Gly	Asp	Asp 90		Ala	Ala	۷a۱	Va1 95	
Arg	Pro	Glu	Gly 100		Pro	Arg	Phe	Tyr 105	Pro	Asp	Glu	Glu	Gly 110	Pro	Lys
His	Trp	Thr 115	Lys	Glu	Arg	His	G1n 120	Phe	Leu	Met	Glu	Leu 125			G٦ι
Ala	Leu 130	Thr	Phe	Ala	Arg	Asn 135		Gly	Ala	Asp	Tyr 140		Leu	Phe	Ala
Asp 145	Thr	Asp	Asn	Ile	Leu 150	Thr	Asn	Asn	Gln	Thr 155		Arg	Leu	Leu	Met 160
Gly	Gln	Gly	Leu	Pro 165	Val	Val	Ala	Pro	Met 170	Leu	Asp	Ser	Gln	Thr 175	Tyr
Tyr	Ser	Asn	Phe 180	Trp	Cys	Gly	Ile	Thr 185	Pro	Gln	Gly	Tyr	Tyr 190	Arg	Arg
Thr	Ala	G1u 195	Tyr	Phe	Pro	Thr	Lys 200	Asn	Arg	Gln	Arg	Arg 205	Gly	Ċys	Phe
Arg	Val 210	Pro	Met	Val	His	Ser 215	Thr	Phe	Leu	Ala	Ser 220	Leu	Arg	Ala	Glu
Gly 225	Ala	Asp	Gln	Leu	A1a 230	Phe	Tyr	Pro	Pro	His 235	Pro	Asn	Tyr	Thr	Trp 240
				245	Ile				250					255	_
			260		Cys			265					270		
		275			Gln		280					285			
	290					295					300				
305					Pro 310					315					320
Glu	Val	Phe	Val	Ile 325	Ser	Leu	Ala	Arg	Arg 330	Pro	Asp	Arg	Arg	G1u 335	Arg

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Met Leu Ala Ser Leu Trp Glu Met Glu Ile Ser Gly Arg Val Val Asp
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                                 345
                                                     350
Ala Val Asp Gly Trp Met Leu Asn Ser Ser Ala Ile Arg Asn Leu Gly
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Val Asp Leu Leu Pro Gly Tyr Gln Asp Pro Tyr Ser Gly Arg Thr Leu
                        375
                                            380
Thr Lys Gly Glu Val Gly Cys Phe Leu Ser His Tyr Ser Ile Trp Glu
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                                        395
Glu Val Val Ala Arg Gly Leu Ala Arg Val Leu Val Phe Glu Asp Asp
                405
                                    410
Val Arg Phe Glu Ser Asn Phe Arg Gly Arg Leu Glu Arg Leu Met Glu
            420
                                425
Asp Val Glu Ala Glu Lys Leu Ser Trp Asp Leu Ile Tyr Leu Gly Arg
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Lys Gln Val Asn Pro Glu Lys Glu Thr Ala Val Glu Gly Leu Pro Gly
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Leu Val Val Ala Gly Tyr Ser Tyr Trp Thr Leu Ala Tyr Ala Leu Arg
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Leu Ala Gly Ala Arg Lys Leu Leu Ala Ser Gln Pro Leu Arg Arg Met
                                    490
Leu Pro Val Asp Glu Phe Leu Pro Ile Met Phe Asp Gln His Pro Asn
                                505
Glu Gln Tyr Lys Ala His Phe Trp Pro Arg Asp Leu Val Ala Phe Ser
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Ala Gln Pro Leu Leu Ala Ala Pro Thr His Tyr Ala Gly Asp Ala Glu
                        535
                                            540
Trp Leu Ser Asp Thr Glu Thr Ser Ser Pro Trp Asp Asp Ser Gly
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_		_			-	att Ile	-	-	-		-	-				144
						tat Tyr 55		-	-	-				-	_	192
		-	-	-		tgt Cys									-	240
	_	_	_			aaa Lys	-		-							288
	_	_			-	agt Ser	_		_	_				_	-	336
			-	-	-	gat Asp	_	_	-					_		384
		Leu	Ala		Lys	gca Ala 135	Cys	Пе	Pro	Tyr						432
-	-					atc Ile	_									480
						gct Ala				_						528
atg	tat	gtg	ctt	gga	atg	gca	gaa	gaa	ttt	aaa	ggt	gaa	att	gca	gtc	576

Met	Tyr	Val	Leu 180	Gly	Met	Ala	Glu	G1u 185	Phe	Lys	Gly	Glu	Ile 190	Ala	Val	
				cct Pro									-	_	-	624
				ggt Gly												672
-	_	_	_	tat Tyr					_			_				720
		-		gat Asp 245	_					-	-			_		768
	-	_		gca Ala							_			-		816
				tac Tyr		-	-	_	-				-			.864
				gaa Glu								-				912
	Arg			gct Ala	Val	Glu	Glu		Phe	-	Пe	-	-	-		960
	_	-	_	gtt Val 325	-		_			-			_		_	1008
		Gly	-	gat Asp			_				-	_		_	_	1056
ggt	999	aat	gtc	gga	tat	gga	gag	cct	tct	gat	cag	gca	gat	gtg	gtg	1104

55

Gly Gly Asn Val Gly Tyr Gly Glu Pro Ser Asp Gln Ala Asp Val Val 355 360 365

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Leu Gly Gly Pro Gly Ile Glu Ser Gln Cys Arg Lys Val Asp Ile Ile

Ala Asp Ala Ala Tyr Ser Ile Phe Gln Lys Pro Lys Ser Phe Thr Gly

220

240

235

215

230

Asn	Phe	Väl	IJе	Asp 245		Asn	Пe	Leu	Lys 250		Glu	Gly	Ile	G1u 255		
Phe	Asp	Val	Tyr 260	Ala	Ile	Lys	Pro	G1y 265		Pro	Leu	Gln	Pro 270			
Phe	Leu	Asp 275	Glu	Tyr	Pro	Glu	Ala 280	Va1	Ser	Lys	Lys	Val 285	Glu	Ser	Thr	
Gly	Ala 290	Val	Pro	Glu	Phe	Lys 295	Glu	Glu	Lys	Leu	G1n 300	Leu	G1n	Pro	Lys	
Pro 305	Arg	Ser	Gly	Ala	Val 310	Glu	Glu	Thr	Phe	Arg 315	Пe	Val	Lys	Asp	Ser 320	
Leu	Ser	Asp	Asp	Val 325	Val	Lys	Ala	Thr	G1n 330	Ala	Пe	Tyr	Leu	Phe 335	Glu	
Leu	Ser	Gly	G1u 340	Asp	Gly	Gly	Thr	Trp 345	Phe	Leu	Asp	Leu	Lys 350	Ser	Lys	
		355	Val				360			,		365	•		Val	
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						gac Asp				Leu						288
						gcc Ala										336
						agc Ser										384
						ttt Phe 135										432
						cct Pro										480
						tcc Ser										528
		Пe				cac His	Ser									576
	Glu					cgt Arg										624
Thr	ctc Leu 210	ctc Leu	ttc Phe	tac Tyr	ttg Leu	ctg Leu 215	tcg Ser	atc Ile	gcg Ala	Ala	gtg Val 220	gcg Ala	ctg Leu	atg Met	ttc Phe	672

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_						_	-	_		tcc Ser		_	_	-	_	768
	_	-	-	-	-					ggt Gly	_	_	-	•	_	816
_						_		_		tgg Trp		-			•	864
		_	-		-				-	cca Pro		_	-			912
										gag Glu 315		_			-	960
-	_	-								ctc Leu	_	_				1008
						-			_	gtg Val		-	_	_	-	1056
	-		-			_		-	-	aca Thr	_	_	_	_	-	1104
										gac Asp						1152
										tgc Cys 395	_	-	-	-		1200

			atg Met							Tyr					Thr	1248
			atc Ile 420									-		•	•	1296
			999 Gly										Ala			1344
	_	-	aac Asn	-	-		_	tga *								1371
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Leu	Cys	Gly	Ser 20	Ala	Pro	Cys	Пe	Leu 25	Cys	Ser	Cys	Cys	Pro 30	Ala	Ser	
Arg	Asn	Ser 35	Thr	Val	Ser	Arg	Leu 40		Phe	Thr	Phe	Phe 45		Phe	Leu	
Gly	Val 50		Val	Ser	Ile	Ile 55	. •	Leu	Ser	Pro	G1 <i>y</i> 60		Glu	Ser	Gln	
Leu 65		Lys	Leu	Pro	Trp 70		Cys	Glu	Glu	Gly 75		Gly	Пe	Pro	Thr 80	
	Leu	Gln	Gly	His 85	. •	Asp	Cys	Gly			Leu	Gly	Tyr			
Val	Tyr	Arg	Met 100		Phe	Ala	Thr	Ala 105	90 Ala	Phe	Phe	Phe	Phe 110	95 Phe	Thr	
Leu	Leu	Met	Leu	Cys	Val	Ser	Ser		Arg	Asp	Pro	Arg		Ala	Ile	

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Gln	Asn 130		Phe	Trp	Phe	Phe 135		Phe	Leu	He	Leu 140	Val	Gly	Leu	Thr
Val 145		Ala	Phe	Tyr	Ile 150		Asp	Gly	Ser	Phe 155	Thr	Asn	Пe	Trp	Phe
Tyr	Phe	Gly	Val	Val 165	Gly	Ser	Phe	Leu	Phe 170	Ile	Leu	Пe	Gln	Leu 175	Val
Leu	Leu	Ile	Asp 180	Phe	Ala	His	Ser	Trp 185		Gln	Arg	Trp	Leu 190	Gly	Lys
Ala	Glu	G1u 195	Cys	Asp	Ser	Årg	Ala 200	Trp	Tyr	Ala	Gly	Leu 205	Phe	Phe	Phe
Thr	Leu 210	Leu	Phe	Tyr	Leu	Leu 215	Ser	Пe	Ala	Ala	Val 220	Ala	Leu	Met	Phe
225					230					235				Phe	240
Ser	Leu	Asn	Leu	Thr 245	Phe	Cys	Val	Cys	Va1 250	Ser	Ile	Ala	Ala	Va1 255	Leu
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		275					280					285		Ser	
	290					295					300			Gly	
305					310					315			-	Trp	320
				325					330					Leu 335	
			340			•		345					350	Met	
		355					360					365		Gln	
	370					375					380			Asp	
385					390					395				Ala	400
				405					410					G1u 415	
Arg	Lys	Met	I1e 420	Ser	Thr	Trp		A1a 425	Val	Trp	Val	Lys	Ile 430	Cys	Ala
Ser		A1 a 435	Gly	Leu	Leu		Tyr 440	Leu	Trp	Thr	Leu	Va1 445	Al a'	Pro	Leu
Leu	Leu 450	Arg	Asn	Arg	•	Phe 455	Ser								

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acc tac ctt gca tct aaa gca tgt att cct tat ttg aaa aag agc aaa

Thr Tyr Leu Ala Ser Lys Ala Cys Ile Pro Tyr Leu Lys Lys Ser Lys

	130			135					140						
	Ala			He		cca Pro							gtt Val 160	48	30
			Cys										tct Ser	52	28
						gaa Glu 185							-	57	⁷ 6
						ata Ile								62	24
						cag Gln								67	'2
						caa Gln	_			-				72	<u>'</u> 0
						tta Leu								76	8
						ggt Gly 265								81	.6
						gtt Val								86	4
Gly						gag G1u								91	2
					-	aca Thr		-		-	_	-		96	0

305 310 315 320

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ctc agt gat gat gtt gtt aaa gcc act caa gca atc tat ctg ttt gaa 1008 Leu Ser Asp Asp Val Val Lys Ala Thr Gln Ala Ile Tyr Leu Phe Glu 325 330 335 ctc tcc ggt gaa gat ggt ggc acg tgg ttt ctt gat ctg aaa agc aag 1056 Leu Ser Gly Glu Asp Gly Gly Thr Trp Phe Leu Asp Leu Lys Ser Lys 340 345 ggt ggg aat gtc gga tat gga gag cct tct gat cag gca gat gtg gtg 1104 Gly Gly Asn Val Gly Tyr Gly Glu Pro Ser Asp Gln Ala Asp Val Val 355 360 365 atg agt atg act act gat gac ttt gta aaa atg ttt tca ggg aaa cta 1152 Met Ser Met Thr Thr Asp Asp Phe Val Lys Met Phe Ser Gly Lys Leu 370 375 380 aaa cca aca atg gca ttc atg tca ggg aaa ttg aag att aaa ggt aac 1200 Lys Pro Thr Met Ala Phe Met Ser Gly Lys Leu Lys Ile Lys Gly Asn 385 390 395 atg gcc cta gca atc aaa ttg gag aag cta atg aat cag atg aat gcc 1248 Met Ala Leu Ala Ile Lys Leu Glu Lys Leu Met Asn Gln Met Asn Ala 405 410 415

aga ctg tga 1257 Arg Leu *

<210> 38 <211> 418 <212> PRT <213> Homo sapiens

<400> 38

WO 01/29221

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	50					55					60				
Gly 65	Gly	Lys	Ala	Leu	Pro 70	Cys	Ile	Val	Asp	Va1 75	Arg	Asp	Glu	Gln	Glr 80
Ile	Ser	Ala	Ala	Va1 85	Glu	Lys	Ala	Ile	Lys 90	Lys	Phe	Gly	Gly	I1e 95	Asp
Ile	Leu	Val	Asn 100	Asn	Ala	Ser	Ala	Ile 105		Leu	Thr	Asn	Thr 110	Leu	Asp
Thr	Pro	Thr 115	Lys	Arg	Leu	Asp	Leu 120	Met	Met	Asn	Val	Asn 125	Thr	Arg	Gly
	130					135					140		Lys		•
145					150					155			Asn		160
•				165					170			-	Gly	175	
	·		180	-				185		-			Ile 190		
		195	·				200					205	Met	,	
	210	•		•		215			•	_	220		Asp		
225	•				230				-	235			Phe		240
				245					250				Ile	255	
			260					265					Pro 270		
		275		Ť			280			_	•	285	Glu		
-	290					295					300		Gln		
305					310					315			Lys		320
				325					330				Leu	335	
	·		340	•				345					Lys 350		
•	•	355		·	•	•	360			•		365	Asp		
	370					375			-		380		Gly		
385					390			-	-	395			Lys		400
Met	Ala	Leu	Ala	He	Lys	Leu	Glu	Lys	Leu	Met	Asn	Gln	Met	Asn	Ala

65

405 410 415 Arg Leu <210> 39 <211> 627 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(627) <400> 39 atg gtg ttc tac ttc acc agc agc gtt aat tca tct gcc tac act 48 Met Val Phe Tyr Phe Thr Ser Ser Ser Val Asn Ser Ser Ala Tyr Thr 5 att tac atg gga aaa gat aaa tat gaa aat gaa gat ctg atc aag cat 96 Ile Tyr Met Gly Lys Asp Lys Tyr Glu Asn Glu Asp Leu Ile Lys His 20 25 30 ggc tgg cct gaa gat atc tgg ttt cat gtg gac aaa ctc tct tcg gct 144 Gly Trp Pro Glu Asp Ile Trp Phe His Val Asp Lys Leu Ser Ser Ala 35 40 cat gta tac ctt cga tta cat aag gga gag aat ata gaa gac atc cca 192 His Val Tyr Leu Arg Leu His Lys Gly Glu Asn Ile Glu Asp Ile Pro 50 55 60 aag gaa gtg ctg atg gac tgt gcc cac ctt gtg aag gcc aat agc att 240 Lys Glu Val Leu Met Asp Cys Ala His Leu Val Lys Ala Asn Ser Ile 65 70 75 caa ggc tgc aag atg aac aac gtt aat gtg gta tat acg ccg tgg tct 288 Gln Gly Cys Lys Met Asn Asn Val Asn Val Val Tyr Thr Pro Trp Ser 85 90 95 aac ctg aag aaa aca gct gac atg gat gtg ggg cag ata ggc ttt cac 336 Asn Leu Lys Lys Thr Ala Asp Met Asp Val Gly Gln Ile Gly Phe His 100 105 110 agg cag aag gat gta aaa att gtg aca gtg gag aag aaa gta aat gag 384 Arg Gln Lys Asp Val Lys Ile Val Thr Val Glu Lys Lys Val Asn Glu

		115					120					125					
		Asn	cga Arg													4	32
	Ala		aaa Lys													4.	80
			cag Gln													5	28
			atg Met 180	_	_			_					_		_	57	76
			tct Ser													62	24
taa *																62	27
	<2 <2	210> 211> 212> 213>	208) sar	oiens									•			
Mot		100>		Dha	The	Con	Can	دمع	V-1	1	Can		۸٦.	T	Th		
1			Tyr	5					10	•				15			
He	lyr	Met	Gly 20	Lys	Asp	Lys	Tyr	G1u 25	Asn	Glu	Asp	Leu	Ile 30	Lys	His		
Gly	Trp	Pro 35	Glu	Asp	Ile		Phe 40	His	Val	Asp	Lys	Leu 45	Ser	Ser	Ala		
His	Val 50		Leu	Arg				Gly	Glu		11e 60		Asp	Ile	Pro		
Lys 65		Val	Leu	Met			Ala	His	Leu			Ala	Asn	Ser	Ile 80		
	Gly	Cys	Lys	Met	-	Asn	Val	Asn	Val		Tyr	Thr	Pro	Trp			

67

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				85					90					95		
Asn	Leu	Lys	Lys 100	Thr	Ala	Asp	Met	Asp 105	Val	Gly	Gln	Ile	Gly 110		His	
Arg	G1n	Lys 115		Val	Lys	Ile	Val 120		Val	Glu	Lys	Lys 125	Val	Asn	Glu	
Ile	Leu 130	Asn	Arg	Leu	Glu	Lys 135	Thr	Lys	Val	Glu	Arg 140	Phe	Pro	Asp	Leu	
Ala 145	Ala	Glu	Lys	Glu	Cys 150		Asp	Arg	Glu	G1u 155	Arg	Asn	Glu	Lys	Lys 160	
Ala	Gln	Ile	Gln	G1u 165	Met	Lys	Lys	Arg	G1u 170	Lyŝ	Glu	Glu	Met	Lys 175	_	
Lys	Arg	Glu	Met 180	Asp	Glu	Leu	Arg	Ser 185		Ser	Ser	Leu	Met 190	Lys	Val	
G1u	Asn	Met 195	Ser	Ser	Asn	Gln	Asp 200	-	Asn ·	Asp	Ser	Asp 205	Glu	Phe	Met	
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	<2	220> 221> 222>	CDS (1)	(4	174)											
	<2	222>	mis((1). n =	(4	174)											
		<00														
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											gtc Val					. 96
											nag Xaa					144
											999 61 v	_	_	-	-	192

	50					55					60					
	_	tgc Cys	-		-							_		-		240
	-	cgc Arg	-			-				_	-	-	_			288
		ggc Gly														336
		aat Asn 115							-	-			_	_	-	384
	_	aat Asn		-	_		-	_	_		-	_				432
		ctt Leu		-	-	_				-	Ser	_	tga *			474
	<2 <2	210> 21 1 > 212> 213>	157 PRT	o sap	oiens	5										
	<2 <2	220> 221> 222> 223>	(1).	(]		iino	Acid	i								
Met 1		100> G1y	-	Leu 5	Gly	Arg	Ala	Ala	Ala 10	Ala	Leu	Leu	Arg	Trp 15	Arg	
	Cys	Ala	G1 <i>y</i> 20		Gly	Gly	Leu	Trp 25		Pro	Val	Val	Arg 30		Ala	
Gly	Ser	A1 a 35		Gly	Gly	Gly	Gly 40		Ala	Xaa	Xaa	Leu 45		Ala	Leu	

Val Lys Lys Asp Lys Val Val Val Phe Leu Lys Gly Thr Pro Glu Gln 50 55 60 Pro Gln Cys Gly Phe Ser Asn Ala Val Val Gln Ile Leu Arg Leu His 70 Gly Val Arg Asp Tyr Ala Ala Tyr Asn Val Leu Asp Asp Pro Glu Leu 90 Arg Gln Gly Ile Lys Asp Tyr Ser Asn Trp Pro Thr Ile Pro Gln Val 105 Tyr Leu Asn Gly Glu Phe Val Gly Gly Cys Asp Ile Leu Leu Gln Met 120 125 His Gln Asn Gly Asp Leu Val Glu Glu Leu Lys Lys Leu Gly Ile His 135 140 Ser Ala Leu Leu Asp Glu Lys Lys Asp Gln Asp Ser Lys 145 150 <210> 43 <211> 1032 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1032) <400> 43 48 Met Gly Gly Pro Arg Gly Ala Gly Trp Val Ala Ala Gly Leu Leu Leu ggc gcg ggc gcc tgc tac tgc att tac agg ctg acc cqq ggt cgg cgg 96 Gly Ala Gly Ala Cys Tyr Cys Ile Tyr Arg Leu Thr Arg Gly Arg Arg 20 25 30 cgg ggc gac cgc gag ctc ggg ata cgc tct tcg aag tcc gca ggt gcc 144 Arg Gly Asp Arg Glu Leu Gly Ile Arg Ser Ser Lys Ser Ala Gly Ala 35 40 ctg gaa gaa ggg acg tca gag ggt cag ttg tgc ggg cgc tcg gcc cgg 192 Leu Glu Glu Gly Thr Ser Glu Gly Gln Leu Cys Gly Arg Ser Ala Arg 50 55 60 cct cag acg gga ggt acc tgg gag tca cag tgg tcc aag acc tcg cag 240 Pro Gln Thr Gly Gly Thr Trp Glu Ser Gln Trp Ser Lys Thr Ser Gln 65 70 75

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			ggt Gly		-	_			~	•	288
			tac Tyr					_		-	336
			att Ile	-			-	-			384
			cgt Arg 135								432
			aac Asn								480
			gtg Val								528
			tgt Cys								576
			gga Gly								624
			atg Met 215								672
		Thr	aat Asn								720
	Asn		gaa Glu								768

	gcc Ala											-	-		-	816
-	aag Lys					-	-		-			_			-	864
	tgc Cys 290								-	-	_					912
-	ggt Gly					_				-		_	-	_		960
	aga Arg															1008
_	aca Thr						tga *			-						1032
	<2 <2	210> 211> 212> 213>	343	o sap	oiens	5										
	<4	+ 00>	44													
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Gly	Ala	Gly	A1a 20	Cys	Tyr	Cys	Ile	Tyr 25	Arg	Leu	Thr	Arg	Gly 30	Arg	Arg	
Arg	Gly	Asp 35	Arg	G1u	Leu	Gly	Ile 40	Arg	Ser	Ser	Lys	Ser 45	Ala	Gly	Ala	
Leu	G1u 50		Gly	Thr	Ser	G1u 55		Gln	Leu	Cys	Gly 60		Ser	Ala	Arg	
65	Gln				70	Trp				75	Ser				80	
Pro	Glu	Asp		Thr 85	Asp	Gly	Ser	Tyr	Asp 90	Asp	Val	Leu	Asn	Ala 95	Glu	

Gln Leu Gln Lys Leu Leu Tyr Leu Leu Glu Ser Thr Glu Asp Pro Val 105 Ile Ile Glu Arg Ala Leu Ile Thr Leu Gly Asn Asn Ala Ala Phe Ser 120 Val Asn Gln Ala Ile Ile Arg Glu Leu Gly Gly Ile Pro Ile Val Ala 135 140 Asn Lys Ile Asn His Ser Asn Gln Ser Ile Lys Glu Lys Ala Leu Asn 150 155 Ala Leu Asn Asn Leu Ser Val Asn Val Glu Asn Gln Ile Lys Ile Lys 170 175 Ile Tyr Ile Ser Gln Val Cys Glu Asp Val Phe Ser Gly Pro Leu Asn 185 Ser Ala Val Gln Leu Ala Gly Leu Thr Leu Leu Thr Asn Met Thr Val 200 Thr Asn Asp His Gln His Met Leu His Ser Tyr Ile Thr Asp Leu Phe 215 220 Gln Val Leu Leu Thr Gly Asn Gly Asn Thr Lys Val Gln Val Leu Lys 225 230 235 Leu Leu Leu Asn Leu Ser Glu Asn Pro Ala Met Thr Glu Gly Leu Leu 245 250 Arg Ala Gln Val Asp Ser Ser Phe Leu Ser Leu Tyr Asp Ser His Val 260 265 270 Ala Lys Glu Ile Leu Leu Arg Val Leu Thr Leu Phe Gln Asn Ile Lys 275 280 285 Asn Cys Leu Lys Ile Glu Gly His Leu Ala Val Gln Pro Thr Phe Thr 295 300 Glu Gly Ser Leu Phe Phe Leu Leu His Gly Glu Glu Cys Ala Gln Lys 310 315 Ile Arg Ala Leu Val Asp His His Asp Ala Glu Val Lys Glu Lys Val 325 330 335 Val Thr Ile Ile Pro Lys Ile 340 <210> 45 <211> 1335 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1335) <221> misc feature <222> (1)...(1335)

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gtt cac att Val His Ile 35	Phe Ile S	Ser Leu V				•	-	144
ggt gtt tta Gly Val Leu 50								192
gaa ttg gac Glu Leu Asp 65	•		_				-	240
atc gta tcc Ile Val Ser			-	-	-		-	288
ctc aga aag Leu Arg Lys	-	-	-					336
aaa gcc atc Lys Ala Ile 115	Ser Ser A	Ala Pro P	•	•	•			384
ttt gcc atc Phe Ala Ile 130								132
agc ctg gga Ser Leu Gly 145	Thr Ala G						3 3	180
gaa tat aag	ccc ctt t	cg ggc a	tt cgg	tac atg	tgg tcg	tac cat	tta 5	528

Glu	Tyr	Lys	Pro	Leu 165	Ser	Gly	Ile	Arg	Tyr 170	Met	Trp	Ser	Tyr	His 175	Leu	
				tgg Trp											-	576
		-		gca Ala		_		-				_	_			624
-			-	cat His				-							ttc Phe	672
				acc Thr												720
		_	-	atc Ile 245		_	-		-			_	-		-	768
-			-	ttg Leu				-		-	_	-		-	-	816
		_		gac Asp			_					_		_		864
			_	att Ile				-		-			•		•	912
•				ttg Leu		-			•							960
-		_	Asp	ttc Phe 325						_					_	1008
ttc	act	gtt	ttt	gga	gga	ctc	atg	gct	ttt	aac	tac	aat	cgg	gca	ttc	1056

cag gtg tgg gca gtc cct ctg tta ttg gta gct ttt ttt gcc tac tta Gln Val Trp Ala Val Pro Leu Leu Leu Val Ala Phe Phe Ala Tyr Leu 355 gta gcc cat agt ttt tta tct gtg ttt gaa act gtg ctg gat gca ctt Val Ala His Ser Phe Leu Ser Val Phe Glu Thr Val Leu Asp Ala Leu 370 ttc ctg tgt ttt gct gtt gat ctg gaa aca aat gat gga tcg tca gaa Phe Leu Cys Phe Ala Val Asp Leu Glu Thr Asn Asp Gly Ser Ser Glu 385 aag ccc tac ttt atg gat caa gaa ttt ctg agt ttc gta aaa agg agc Lys Pro Tyr Phe Met Asp Gln Glu Phe Leu Ser Phe Val Lys Arg Ser 405 aac aaa tta aac aat gca agg gca cag cag gac aag cac tca tta agg Asn Lys Leu Asn Asn Ala Arg Ala Gln Gln Asp Lys His Ser Leu Arg 420 aat gag gag gag aca gaa ctc cag gcc att gtg aga tag Asn Glu Glu Gly Thr Glu Leu Gln Ala Ile Val Arg 435 1104	
Val Ala His Ser Phe Leu Ser Val Phe Glu Thr Val Leu Asp Ala Leu 370 375 380 1200 ttc ctg tgt ttt gct gtt gat ctg gaa aca aat gat gga tcg tca gaa Phe Leu Cys Phe Ala Val Asp Leu Glu Thr Asn Asp Gly Ser Ser Glu 385 390 395 400 1248 Lys Pro Tyr Phe Met Asp Gln Glu Phe Leu Ser Phe Val Lys Arg Ser 405 410 415 aac aaa tta aac aat gca agg gca cag cag gac aag cac tca tta agg Asn Lys Leu Asn Asn Ala Arg Ala Gln Gln Asp Lys His Ser Leu Arg 420 425 430 1335 Asn Glu Glu Gly Thr Glu Leu Gln Ala Ile Val Arg *	
Phe Leu Cys Phe Ala Val Asp Leu Glu Thr Asn Asp Gly Ser Ser Glu 385 390 395 400 aag ccc tac ttt atg gat caa gaa ttt ctg agt ttc gta aaa agg agc Lys Pro Tyr Phe Met Asp Gln Glu Phe Leu Ser Phe Val Lys Arg Ser 405 410 415 aac aaa tta aac aat gca agg gca cag cag gac aag cac tca tta agg Asn Lys Leu Asn Asn Ala Arg Ala Gln Gln Asp Lys His Ser Leu Arg 420 425 430 aat gag gag gga aca gaa ctc cag gcc att gtg aga tag Asn Glu Glu Gly Thr Glu Leu Gln Ala Ile Val Arg *	
Lys Pro Tyr Phe Met Asp Gln Glu Phe Leu Ser Phe Val Lys Arg Ser 405 410 415 aac aaa tta aac aat gca agg gca cag cag gac aag cac tca tta agg 1296 Asn Lys Leu Asn Asn Ala Arg Ala Gln Gln Asp Lys His Ser Leu Arg 420 425 430 aat gag gag gga aca gaa ctc cag gcc att gtg aga tag 1335 Asn Glu Glu Gly Thr Glu Leu Gln Ala Ile Val Arg *	
Asn Lys Leu Asn Asn Ala Arg Ala Gln Gln Asp Lys His Ser Leu Arg 420 425 430 aat gag gag gga aca gaa ctc cag gcc att gtg aga tag Asn Glu Glu Gly Thr Glu Leu Gln Ala Ile Val Arg *	
Asn Glu Glu Gly Thr Glu Leu Gln Ala Ile Val Arg *	
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Leu Ser Leu Ala Met Met Phe Thr Phe Arg Phe Ile Thr Thr Leu Leu	
20 25 30 Val His Ile Phe Ile Ser Leu Val Ile Leu Gly Leu Leu Phe Val Cys	

		35					40					45			
Gly	Va1 50	Leu	Trp	Trp	Leu	Tyr 55	Tyr	Asp	Tyr	Thr	Asn 60	Asp	Leu	Ser	Ιle
G1u 65	Leu	Asp	Thr	Glu	Arg 70	Glu	Asn	Met	Lys	Cys 75	Val	Leu	Gly	Phe	A1a 80
Ile	Val	Ser	Thr	Gly 85	Ile	Thr	Ala	Val	Leu 90	Leu	Val	Leu	Ile	Phe 95	Val
			Arg 100					105					110		
		115	Ser			•	120					125		·	
	130		Leu			135					140				
Ser 145		Gly	Thr	Ala	Gly 150	Ala	Ala	Gln	Val	Met 155	Glu	Gly	Gly	G1n	Val 160
Glu	Tyr	Lys	Pro	Leu 165	Ser	Gly	He	Arg	Tyr 170	Met	Trp	Ser	Tyr	His 175	Leu
He	Gly	Leu	Ile 180	-	Thr		Glu	Phe 185	He	Leu	Ala	Cys	Gln 190	Gln	Met
Thr	Ile	Ala 195	Gly	Ala	Val	Xaa	Thr 200	Cys	Tyr	Phe	Asn	Arg 205	Ser	Lys	Asn
	210		Asp			215					220				
225			Gly		230					235					240
			Arg	245					250					255	
			A1 a 260					265					270		-
		275	Leu				280					285			
	290		Ala			295		·			300				·
305			Ile		310					315					320
Cys	Phe	Gly	Asp	Phe 325	He	He	Phe	Leu	G1y 330	Lys	Val	Leu	Val	Va1 335	Cys
Phe	Thr	Val	Phe 340	Gly	Gly	Leu	Met	A1a 345	Phe	Asn	Tyr	Asn	Arg 350	Ala	Phe
Gln	Val	Trp 355	Ala	Val	Pro	Leu	Leu 360	Leu	Val	Ala	Phe	Phe 365	Ala	Tyr	Leu
Val	A1a 370	His	Ser	Phe	Leu	Ser 375	Val	Phe	Glu	Thr	Va1 380	Leu	Asp	Ala	Leu
Phe	Leu	Cys	Phe	Ala	Va1	Asp	Leu	Glu	Thr	Asn	Asp	Gly	Ser	Ser	Glu

385 Lys	Pro	Tyr	Phe	Met 405	390 Asp	Gln	Glu	Phe	Leu 410	395 Ser		Val	Lys	Arg 415	400 Ser	
Asn	Lys	Leu	Asn 420		Ala	Arg	Ala	G1n 425		Asp	Lys	His	Ser 430		Arg	
Asn	Glu	G1u 435	Gly	Thr	Glu	Leu	G1n 440	Ala	Ile	Val	Arg					
	<' ₄		351 DNA	o sap	piens	s										
	<'2	220> 221> 222>	CDS	(3	351)											
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						gag G1u										96
						atg Met			-					_		144
						act Thr 55										192
						gat Asp							_			240
	-					aat Asn		-				-		_	-	288
						act Thr										336

78 100 105 110 gaa cat gca tcc taa 351 Glu His Ala Ser * 115 <210> 48 <211> 116 <212> PRT <213> Homo sapiens <400> 48 Met Ala Asp Glu Ala Leu Phe Leu Leu Leu His Asn Glu Met Val Ser 10 Gly Val Tyr Lys Ser Ala Glu Gln Gly Glu Val Glu Asn Gly Arg Cys 25 Ile Thr Lys Leu Glu Asn Met Gly Phe Arg Val Gly Gln Gly Leu Ile 40 Glu Arg Phe Thr Lys Asp Thr Ala Arg Phe Lys Asp Glu Leu Asp Ile 55 Met Lys Phe Ile Cys Lys Asp Phe Trp Thr Thr Val Phe Lys Lys Gln 75 Ile Asp Asn Leu Arg Thr Asn His Gln Gly Ile Tyr Val Leu Gln Asp 90 Asn Lys Phe Arg Leu Leu Thr Gln Met Ser Ala Gly Lys Gln Tyr Leu 100 105 110 Glu His Ala Ser 115 <210> 49 <211> 516 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(516) <400> 49 atg aag aaa tgt ctt ttg ccc gtt ttg att acg tgc atg caa aca gcg 48

Met Lys Lys Cys Leu Leu Pro Val Leu Ile Thr Cys Met Gln Thr Ala

10

15

5

79

_		_	_	_	_	_		-			_	gtg Val 30				96
	_	_			_	_	_				-	cat His	_			144
												aag Lys]	192
					-	_				-	_	tgc Cys		-	2	240
												cga Arg	-		2	288
	-		_									act Thr 110			3	336
			_		-				-	-		tgt Cys	_		3	384
												gga Gly			4	132
												999 Gly			4	180
		ggc Gly								taa *					5	516

<210> 50

<211> 171

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Lys Phe Lys Leu Phe Thr Leu Val Ser Ala Cys Ile Pro Val Phe Arg
20 25 30

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				_	-	gat Asp 55									•	192
						gaa G1u							-	-		240
	-		_	_		aca Thr	-	_	-		-	-			•	288
	_				_	cct Pro	_	_							_	336
	-					gtt Val				-	-	_		-		384
					_	ctg Leu 135					_		_		_	432
						ctg Leu	-	-		-	_	-	_		-	480
_				_		gag Glu		_		_			-			528
	_		_		_	gag G1u			-			_	-	-	_	576
	-	-		-		gac Asp			_					-		624

			cag Gln				-	-	_	_	672
			agc Ser 230				-		-	_	720
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 Pro
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 Leu
 Leu
 Val
 His
 Gly
 Ser
 Pro
 Leu
 Val
 Phe
 Gly
 Gly
 Gly
 Inches
 Inches<

83

100 105 110 Thr Ser Phe Asp Ser Val Val Pro Glu Lys Leu Asp Asp Leu Val Pro 120 115 125 Lys Gly Lys Lys Phe Leu Leu Ser Ile Asn Arg Tyr Glu Arg Lys 135 130 140 Lys Asn Leu Thr Leu Ala Leu Glu Ala Leu Val Gln Leu Arg Gly Arg 150 155 Leu Thr Ser Gln Asp Trp Glu Arg Val His Leu Ile Val Ala Gly Gly 170 Tyr Asp Glu Arg Val Leu Glu Asn Val Glu His Tyr Gln Glu Leu Lys 185 Lys Met Val Gln Gln Ser Asp Leu Gly Gln Tyr Val Thr Phe Leu Arg 195 200 205 Ser Phe Ser Asp Lys Gln Lys Ile Ser Leu Leu His Ser Cys Thr Cys 215 220 Val Leu Tyr Thr Pro Ser Asn Glu His Phe Gly Ile Val Pro Leu Glu 230 235 Ala Met Tyr Met Gln Cys Pro Val Ile Ala Val Asn Ser Gly Gly Pro 245 250 Leu Glu Ser Ile Asp His Ser Val Thr Gly Phe Leu Cys Glu Pro Asp 260 265 Pro Val His Phe Ser Glu Ala Ile Glu Lys Phe Ile Gln Lys Ser His 280 285 Pro <210> 53 <211> 1041 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1041) <221> misc feature <222> (1)...(1041) <223> n = A,T,C or G<400> 53 48 Met Pro Arg Val Phe Val Phe Arg Ala Leu Leu Leu Val Leu Ile Phe 1 15 5 10

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	_	-							_	_		-	-	ctg Leu		192
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_				_			_	_			_	_		cag Gln 95	_	288
_	-	_		_		-					-			atc Ile		336
						-				-	_	_	_	cat His	_	384
_		_		_			_	-			_			gcc Ala		432
	_			_	_		_	-	-	-		-		gac Asp		480
-				_			_		_	-		-		cga Arg 175	-	528
							Val							ttc Phe		576

	cgt Arg									624
	cct Pro									672
	cag G1n								cac His 240	720
	agc Ser									768
	aag Lys 260									816
	gac Asp									864
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Ser	Asp 290		Ala	Val	Thr	Asn 295	Gly	Leu	Arg	Asp	Gly 300	Пe	Val	Phe	Val	
Leu 305	Lys	Cys	Leu	Asp	Phe 310	Ser	Leu	Val	۷a٦	Asn 315	Val	Lys	Lys	Ile	Pro 320	
Phe	He	Ile	Leu	Ser 325	Glu	Glu	Phe	Пe	Asp 330	Pro	Lys	Ser	His	Lys 335	Phe	
Val	Leu	Arg	Leu 340	Gln	Ser	G1u	Thr	Ser 345	Val							
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Glu	Arg	Arg 35	Lys	Lys	Glu	Ala	Asn 40	Lys	Ala	Thr	Arg	A1a 45	Asn	His	Asn	
Arg	Arg 50	Thr	Met	Ala	Asp	Arg 55	Lys	Arg	Ser	Lys	Gly 60	Met	Ile	Pro	Ser	
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													cac His			144
										-			gaa Glu			192
									-	-	-		ctg Leu			240
													ctc Leu			288

					tat Tyr									336
					ttg Leu		-	-		-		_		384
					cct Pro 135							_	-	432
			_		atc Ile			-		_				480
_		_	_	_	atg Met									528
				-	gat Asp		-							576
					gga Gly									624
					tct Ser 215									672
					tca Ser									720
					agt Ser									768
					gtc Val	Phe			_		-			816

-			_	_			ccc Pro				 _	_	864
_	-		_		-		tgg Trp	_			-	_	912
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91

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Tyr Lys Trp Phe Leu Leu Ile Tyr Lys Ile Ser Tyr Ala Thr Gly Ile
                    150
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Val Gly Tyr Met Ala Val Met Phe Thr Leu Phe Gly Leu Asn Leu Leu
                                    170
Phe Lys Ile Lys Pro Glu Asp Ala Met Asp Phe Gly Ile Ser Leu Leu
                                185
Phe Tyr Gly Leu Tyr Tyr Gly Val Leu Glu Arg Asp Phe Ala Glu Met
                             200
                                                 205
Cys Ala Asp Tyr Met Ala Ser Thr Ile Gly Phe Tyr Ser Glu Ser Gly
                        215
                                            220
Met Pro Thr Lys His Leu Ser Asp Ser Val Cys Ala Val Cys Gly Gln
                    230
                                        235
Gln Ile Phe Val Asp Val Ser Glu Glu Gly Ile Ile Glu Asn Thr Tyr
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                                    250
                                                         255
Arg Leu Ser Cys Asn His Val Phe His Glu Phe Cys Ile Arg Gly Trp
                                265
Cys Ile Val Gly Lys Lys Gln Thr Cys Pro Tyr Cys Lys Glu Lys Val
                            280
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Asp Leu Lys Arg Met Phe Ser Asn Pro Trp Glu Arg Pro His Val Met
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                                            300
Tyr Gly Gln Leu Leu Asp Trp Leu Arg Tyr Leu Val Ala Trp Gln Pro
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Met Leu Asp Leu Gln Lys Gln Leu Gly Arg Xaa Gln Xaa Ala Xaa Phe
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10

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48

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									gct Ala 75						240
									ctg Leu						288
									cct Pro						336
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ctc Leu	agc Ser 130	tag *													393
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	35					40				45					
					atg Met 55							-	-		192
		_	_		ttc Phe		_	_		_	-				240
					tca Ser		-				-			•	288
					gca Ala										336
-	 -			-	cac His			_	-			_	_		384
				_	tca Ser 135		_			-	_				432
					cca Pro	_		_					_		480
					999 G1y		-								528
					cca Pro		-			-			-		576
					gca Ala			_							624
					atg Met										672

	210)		•		215					220	ı				
	Asn					Phe						ggt Gly				720
					Lys							ggt Gly				768
				- Ala								atc Ile				816
			Val									gag Glu 285				864
												999 Gly				912
												atc Ile				960
												gga Gly				1008
												tta Leu				1056
												gcc Ala 365				1104
							_		_	Gly		gct Ala				1152
ttg Leu	gtg Val	ggc Gly	aac Asn	aat Asn	ttc Phe	gct Ala	cca Pro	aat Asn	att Ile	ata Ile	ttt Phe	gca Ala	ctt Leu	gct Ala	gga Gly	1200

385 390 395 400 ggc atg ttc ctc tat att tct ctg gca gat atg ttt cca gag atg aat 1248 Gly Met Phe Leu Tyr Ile Ser Leu Ala Asp Met Phe Pro Glu Met Asn 405 410 415 gat atg ctg aga gaa aag gta act gga aga aaa acc gat ttc acc ttc 1296 Asp Met Leu Arg Glu Lys Val Thr Gly Arg Lys Thr Asp Phe Thr Phe 420 425 ttc atg att cag aat gct gga atg tta act gga ttc aca gcc att cta 1344 Phe Met Ile Gln Asn Ala Gly Met Leu Thr Gly Phe Thr Ala Ile Leu 435 440 445 ctc att acc ttg tat gca gga gaa atc gaa ttg gag taa 1383 Leu Ile Thr Leu Tyr Ala Gly Glu Ile Glu Leu Glu * 450 455 460 <210> 62 <211> 460 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(460) <223> Xaa = Any Amino Acid <400> 62 Met Ala Pro Gly Arg Ala Val Ala Gly Leu Leu Leu Leu Ala Ala Ala 1 5 10 Xaa Leu Gly Gly Val Ala Glu Gly Pro Gly Leu Ala Phe Ser Glu Asp 25 Val Leu Ser Val Phe Gly Ala Asn Leu Ser Leu Ser Ala Ala Gln Leu Gln His Leu Leu Glu Gln Met Gly Ala Ala Ser Arg Val Gly Val Pro Glu Pro Gly Gln Leu His Phe Asn Gln Cys Leu Thr Ala Glu Glu Ile 70 75 80 Phe Ser Leu His Gly Phe Ser Asn Ala Thr Gln Ile Thr Ser Ser Lys 90 Phe Ser Val Ile Cys Pro Ala Val Leu Gln Gln Leu Asn Phe His Pro 100 105 110

Cys	Glu	Asp 115		Pro	Lys	His	Lys 120		Arg	Pro	Ser	His 125		Glu	Val
Trp	Gly 130		Gly	Phe	Leu	Ser 135		Thr	Пe	Ile	Asn 140	Leu		Ser	Leu
Leu 145		Leu	He	Leu	Thr 150		Leu	Ile	Lys	Lys 155		Tyr	Phe	Pro	Lys 160
Ile	Leu	Thr	Phe	Phe 165	۷a٦	Gly	Leu	Ala	Ile 170		Thr	Leu	Phe	Ser 175	Asn
Ala	Ile	Phe	Gln 180	Leu	Ile	Pro	Glu	Ala 185		Gly	Phe	Asp	Pro 190		Val
Asp	Ser	Tyr 195		Glu	Lys	Ala	Va1 200		Val	Phe	Gly	Gly 205		Tyr	Leu
Leu	Phe 210	Phe	Phe	Glu	Arg	Met 215		Lys	Met 	Leu	Leu 220	Lys	Thr	Tyr	Gly
G1n 225		Gly	His	Thr	His 230	Phe	Gly	Asn	Asp	Asn 235	Phe	Gĺy	Pro	Gln	G1u 240
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Tyr	Ala	Asn	Pro 260	Ala	Val	Thr	Glu	A1a 265	Asn	Gly	His	Ile	His 270	Phe	Asp
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305					310					Asn 315			•		320
				325					330	Leu				335	
			340					345		His			350	•	
		355					360			Arg		365			
	370					375					380			•	
385					390					11e 395					400
				405					410	Met				415	
Asp	Met	Leu	Arg 420	Glu	Lys	Val	Thr	G1y 425	Arg	Lys	Thr	Asp	Phe 430	Thr	Phe
Phe		I1e 435	Gln	Asn	Ala	Gly	Met 440	Leu	Thr	Gly		Thr 445	Ala	Пe	Leu
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	ctc Leu 50														_	192
	aaa Lys	-	-	_						-	_			_		240
_	tcc Ser					-		_				-	•	_	-	288
	tcc Ser															336
	aca Thr		-	-			_			_				_		384
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	cca Pro	-	-		_		-					-			•	480
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Asp	Ser	Leu	Tyr	Arg 85	His	Asp	Ser	Asp	Thr 90	Pro	Ser	Asp	Ser	Leu 95	Asp		
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										cgg Arg						19	92

						gga Gly								_	_	240
						ttc Phe						_		_		288
						gtg Val								_	-	336
	-	_	_	-	-	atg Met	-		-	_	_	-		-	-	 384
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Αla	Gln	A1a 35	Arg	Arg	Leu	Gln	G1y 40	Asp	Val	Ala	Gly	A1 a 45	Leu	G1u	Asp	
Leu	G1u 50	Arg	Ala	Val	Glu	Leu 55	Ser	Gly	Gly	Arg	Gly 60	Arg	Ala	Ala	Arg	
G]n 55	Ser	Phe	Val	G1n	Arg 70	Gly	Leu	Leu	Ala	Arg 75	Leu	Gln	Gly	Arg	Asp 80	
	Asp	Ala		Arg 85		Phe	Glu	Arg	Ala 90		Arg	Leu	Gly	Ser 95		
Phe	Ala	Arg			Leu	Val	Leu	Leu 105		Pro	Tyr	Ala	Ala 110		Cys	
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PCT/US00/29052

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					ggc Gly 70									240
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Gly Leu Trp Leu Cys Gln Pro Thr Pro Arg Cys Gly Asn Lys Ile Tyr
Asn Pro Ser Glu Gln Cys Cys Tyr Asp Asp Ala Ile Leu Ser Leu Lys
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Glu Thr Arg Arg Cys Gly Ser Thr Cys Thr Phe Trp Pro Cys Phe Glu
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65
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                                                            80
Leu Cys Cys Pro Glu Ser Phe Gly Pro Gln Gln Lys Phe Leu Val Lys
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                                    90
Leu Arg Val Leu Gly Met Lys Ser Gln Cys His Leu Ser Pro Ile Ser
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Leu Gly Ala Pro Val Glu Gly Glu Ala Lys His Trp Glu Pro Phe Arg
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                                 25
                                                                      144
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Lys	Val	Val 35	Ser	Gly	Arg	Ile	Ile 40	Asn	Gly	Tyr	Cys	Arg 45	Gly	Asp	Trp	
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												gag Glu			-	240
-				-	_			-	_		-	aag Lys	_	_	_	288
-		-	_	-				-		-		ggc Gly		-		336
					-			-	-			gag Glu 125			-	384
_	-			-	-							cac His	-	-		432
		-						-				ttg Leu	_	_		480
			-		-	_	-		-		_	gac Asp	_		_	528
												ccc Pro				576
						Asn		_		_		gat Asp 205	-			624
aag	асс	cag	ggc	ссс	agc	acg	999	ctg	gac	tga						657

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Lys Val Val Ser Gly Arg Ile Ile Asn Gly Tyr Cys Arg Gly Asp Trp
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Leu Leu Ser Phe Val Tyr Arg Thr Ser Ser Val Gln Leu His Val Ala
Gly Leu Gln Pro Val Leu Leu Gln Asp Arg Arg Val Glu Asn Val Asp
                    70
Leu Thr Ser Val Val Ser Gly His Leu Asp Tyr Ala Lys Gln Met Asp
Ala Ile Leu Lys Ala Val Gly Ile Arg Thr Lys Pro Gly Trp Asp Glu
           100
                                105
Lys Gly Leu Leu Ala Pro Gly Cys Leu Pro Ser Glu Glu Pro Arg
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Gln Ala Ala Ala Ala Ser Ser Gly Glu Thr Pro His Gln Val Gly
                        135
Gln Thr Gln Gly Pro Ile Ser Gly Asp Thr Ser Lys Leu Ala Met Ser
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Thr Asp Pro Ser Gln Ala Gln Val Pro Val Gly Leu Asp Gln Ser Glu
Gly Ala Ser Leu Pro Ala Ala Ala Ser Pro Glu Arg Pro Pro Ile Cys
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Ser His Gly Met Asp Pro Asn Pro Leu Gly Cys Pro Asp Cys Ala Cys 200

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						gtc Val				-		_		288
						ctc Leu 105	_	_		_		-	-	336
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Leu Ala Tyr Phe Thr Ser Gly Phe Asn Ala Ala Ala Leu Asp Tyr Glu
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Ala Asp Gly Ser Thr Asn Asn Gly Ile Phe Gln Ile Asn Ser Arg Arg
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Trp Cys Ser Asm Leu Thr Pro Asm Val Pro Asm Val Cys Arg Met Tyr.
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                                    90
Cys Ser Asp Leu Leu Asn Pro Asn Leu Lys Asp Thr Val Ile Cys Ala
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Met Lys Ile Thr Gln Glu Pro Gln Gly Leu Gly Tyr Trp Glu Ala Trp
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	cct Pro 50			_						_					_		192
	ctt Leu		-	-	_	_			-				-	-	_		240
	aat Asn			-			_			-			_				288
	gtg Val			-	-								_	_			336
	cag Gln	tga *															345
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_	Trp	Ser	Ser 20		Ala	Phe	Пe	I1e 25		Tyr	Val	Val	Ala 30		Leu		
Ser	Gly	His 35		Asn	Pro	Phe	Leu 40		Tyr	Пе	Ser	Asp 45		Gly	Thr		
ſhr	Pro 50		Glu	Ser	Gly	I1e 55	Phe	Gly	Phe	Met	Ile 60	Asn	Phe	Ser	Ala		
Phe 55	Leu	Gly	Ala		Thr 70	Met	Tyr	Thr	Arg	Tyr 75	Lys	Ile	Val	Gln	Lys 80		

110

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105

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Thr	Ser	Phe 115		Ser	Val	Val	Pro 120		Lys	Leu	Asp	Asp 125		Val	Pro	
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113

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										acc Thr				576
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Arg	G1u 50	Leu	Arg	Gln	Ala	A1a 55	Glu	Cys	G1.y	Pro	Glu 60	Pro	Gly	Val	Ser
Gly 65	Val	Gly	Glu	Leu	I1e 70	Val	Arg	Glu	Leu	Asp 75	Leu	Ala	Ser	Leu	Arg 80
Ser	Val	Arg	Ala	Phe 85	Cys	Gln	Glu	Met	Leu 90	Gln	Glu	Glu	Pro	Arg 95	Leu
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Thr	Glu	Asp 115	Gly	Phe	Glu	Met	Gln 120	Phe	Gly	Val	Asn	His 125	Leu	Gly	His
Phe	Leu 130	Leu	Thr	Asn	Leu	Leu 135	Leu	Gly	Leu	Leu	Lys 140	Ser	Ser	Ala	Pro
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•		-	180	Ť	Leu			185					190		
		195			Thr		200					205			-
	210				Leu	215	•				220				
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_					_	tcg Ser 215	_	_	-			_	-			672
_	_	-			-	ttt Phe			_	-	-				_	720
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		-				gga Gly					-	_		-		864
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	-				-	gta Val				_		_	-			1008
		Pro				ttt Phe										1056
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200

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Lys 225		Val	Leu	Pro	Thr 230		: Ile	. Lei	ı Glu	Arg 235		Ser	Leu	. Leu	G1u 240
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				Trp 405					410					415	
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Met 65		Glu	Met	Tyr	G1u 70		Val	Ser	Asn	Va1 75		Glu	Tyr	Arg	G1u 80	
Phe	Val	Pro	Trp	Cys 85	Lys	Lys	Ser	Leu	Va1 90	Val	Ser	Ser	Arg	Lys 95	Gly	

His	Leu	Lys	Ala 100	Gln	Leu	Glu	Val	Gly 105	Phe	Pro	Pro	Val	Met 110	Glu	Arg		
Tyr	Thr	Ser 115	Ala	۷a۱	Ser	Met	Val 120	Lys	Pro	His	Met	Val 125	Lys	Ala	Val		
Cys	Thr 130	Asp	Gly	Lys	Leu	Phe 135	Asn	His	Leu	Glu	Thr 140	Ile	Trp	Arg	Phe		
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	Ser			165					17û					175			
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cct Pro	gtc Val	atg Met	gaa Glu 100	cgt Arg	tac Tyr	acc Thr	tct Ser	gca Ala 105	gtt Val	tcc Ser	atg Met	gtc Val	aaa Lys 110	cct Pro	cac	336
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Gln	Leu	Ala	Thr	Met 165	Phe	Phe	Asp	Glu	Val 170	Val	Lys	Gln	Asn	Va1 175	Ala	
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	gct Ala															96
gcc	acc	ctg	aag	acc	atc	cgg	aac	ggc	gtt	cat	aag	ata	gac	acg	tac	144

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					gga Gly												288
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Leu	Asn 50	Ala	Ala	Leu	Asp	Leu 55	Leu	Gly	Gly	Glu	Asp 60	Gly	Leu	Cys	Gln	
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	Ser			85					90					95		
	Ile		100					105					110		-	
	Tyr	115					120					125				
	Tyr 130					135					140					
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	Ser			165					170			·	Ser	G1n 175	Arg	
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									-		-	_		atg Met 95	-	288
_		_		_							_			att Ile	-	336
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														gtc Val 175		528
														ctc Leu		576
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Asn 65	Arg	Lys	Val	Leu	Gly 70	Asp	Leu	Пe	Phe	Asn 75	Gln	Pro	Asp	Arg	Arg 80	
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Pro Glu Arg Trp Gly Pro Gly Arg Phe Asp Tyr Trp Gly Asn Ser His
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Gln Ile Met His Leu Leu Ser Val Gly Ser Ile Leu Gln Leu His Ala
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                                                          15
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Arg His Ser Leu Leu Ser Pro Leu Leu Ser Val Thr Ser Phe Arg Arg
             20
                                 25
                                                      30
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Phe Tyr Arg Gly Asp Ser Pro Thr Asp Ser Gln Lys Asp Met Ile Glu
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                             40
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                                                                      192
Ile Pro Leu Pro Pro Trp Gln Glu Arg Thr Asp Glu Ser Ile Glu Thr
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                         55
                                             60
                                                                      240
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Lys Arg Ala Arg Leu Leu Tyr Glu Ser Arg Lys Arg Gly Met Leu Glu
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Lys 145	Asn	Lys	Asn	Lys	Glu 150	Gln	Arg	Leu	Arg	Ala 155		Asp	Leu	Glu	Tyr 160	
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	_		_			999 Gly 55			-	-	-			_	_	192
						aca Thr			-	_		-				240
						cat His										288
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-						_					_	acc Thr				432
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				-		acc Thr 135					_		-		432
_						aac Asn		-							480
	-	-		-		gag Glu	_			 -	-		-		528
-				-		cat His	-	_			_			-	576
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Gly							atg Met				960
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141

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Leu	Pro	Asn	Pro 180		Tyr	His	Cys	Leu 185		Ser	Va1	Ala	Gly 190		Met
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Phe	His	Thr	His	Pro 405	Lys	Xaa	Gln	Glu	Val 410	Gln	Val	Val	Gly	Val 415	Lys
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Ile	Ser 450	His	Phe	Lys	He	Pro 455	Lys	Tyr	Ile	Val	Phe 460	Val	Thr	Asn	Tyr
Pro 465	Leu	Thr	Ile	Ser	G1 <i>y</i> 470	Lys	Ile	Gln	Lys	Phe 475	Lys	Leu	Arg	Glu	G1n 480
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Pro	Trp 50	Ala	Leu	Gln	Thr	Leu 55	Ala	Val	Asp	Tyr	Gly 60	Ser	Tyr	Ile	Arg		
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Arg	ыу	ыу	Ser 20	Arg	Pne	Leu	АІа	1nr 25	Ser	I те	Ala	Ser	30	ASP	Asp	,	
aac	agc	ctc	t.t.c	atc	tať	gac	tac	aat	act	gca	gaa	aaa	aaa	tca	caa	144	
											Glu					27.	
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					Пe					Lys					ctg Leu	288
						agg Arg			Thr						gcc Ala	336
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cac lis 225	tgc Cys	tgt Cys	cac His	Leu	gcc Ala 230	agt Ser	ctg Leu	cag G1n	Glu	ctg Leu 235	gtg Val	gac Asp	ccc Pro	cag Gln	gcc Ala 240	720

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									atg Met							1056
									aag Lys							1104
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Gly	Asp	Gln	Trp	G1n 325	Ser	Val	Pro	G1u	Ser 330	Thr	Val	Leu	Lys	Lys 335		
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Pro Gly Glu Asp Asp Lys Tyr Asn Ile Gly Ile Ile Glu Glu Asn Trp
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Gln Leu Ser Gln Phe Trp Tyr Ser Gln Glu Thr Ala Leu Gln Leu Ala
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Gln Glu Ala Ile Ala Ala Val Gly Glu Gly Gly Arg Ile Ala Cys Val
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Ser Ala Pro Ser Val Tyr Gln Lys Leu Arg Glu Leu Cys Arg Glu Asn
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Phe Ser Ile Tyr Ile Phe Glu Tyr Asp Lys Arg Phe Ala Met Tyr Gly
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Glu Glu Phe Ile Phe Tyr Asp Tyr Asn Asn Pro Leu Asp Leu Pro Glu
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Arg Ile Ala Ala His Ser Phe Asp Ile Val Ile Ala Asp Pro Pro Tyr
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Leu Ser Glu Glu Cys Leu Arg Lys Thr Ser Glu Thr Val Lys Tyr Leu
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Thr Arg Gly Lys Ile Leu Leu Cys Thr Gly Ala Ile Met Glu Glu Gln
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		Thr	aag Lys													192
	Asp		ggc Gly													240
			tgc Cys				tag *									264
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vai	ser	ınr	A1a 20	vaı	Pro	Lys		Pro 25	Ala	Gly	Pro	Lys	Lys 30	GIn	Cys	
Trp	Cys	Gly 35	Glu	Cys	Thr		Trp 40	Ser	Gly	Val	Trp	Thr 45	Cys	Asp	Asp	
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_	_				cgt Arg	-	_		-		-	_	_	_	336
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				-	gct Ala		-		-		-	-		-	528
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		aga Arg									912
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		gaa Glu									1008
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		cga Arg 390									1200
	Lys	aaa Lys		Leu							1248

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ggc Gly										agt Ser					1728
cag Gln	Gly				-	Lys						-		-	1776

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Asp	Ala	Cys 355	Glu	Asp	Val	Cys	Asp 360	Lys	Pro	Leu	Leu	Tyr 365	Glu	Ile	Gly
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Leu	Leu	G1n 435	Arg	He	Пe	Val	G1u 440	Leu	Val	Glu	Phe	11e 445	Ser	Pro	Lys
Thr	Pro 450	Lys	Pro	Gly	Glu	Leu 455	Gly	Gly	Arg	Ile	Ser 460	Gly	Ser	Val	Ala
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Phe	Пe	Pro	Cys	G1u 485	Asn	Glu	Lys	Ile	Ser 490	Lys	Gln	Leu	Ḥis	Leu 495	Cys
Tyr	Asn	Ile	Va1 500	Lys	Asp	Arg	Tyr	Va1 505	Arg	Val	Ser	Asn	Asn 510	Asn	Gln

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Gly	Leu	Lys	Val	Asp 565	Ser	Ile	Ser	Ile	Arg 570	Thr	Ser	Ser	Gln	Thr 57.5	Phe	
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Glu	Leu	Thr 595	Gly	Asp	Asn	Ser	Leu 600	His	Ser	Tyr	Ala	Asp 605	Phe	Ser	Gly	
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										cag Gln	•	336
							-		~	gtt Val		384
										agg Arg		432
										tgt Cys		480
										agc Ser 175		528
	_	_	-	_	_	_	_		-	aga Arg		576
ggc Gly	taa *											585

<210> 114

<211> 194

<212> PRT

<213> Homo sapiens

<400> 114

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Ser Glu Ser Ser Asn Trp Gly Cys Tyr Gly Asn Ile Gln Ser Leu Asp
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Thr Pro Gly Ala Ser Cys Gly Ile Gly Arg Arg His Gly Leu Asn Tyr
                            40
Cys Gly Val Arg Ala Ser Glu Arg Leu Ala Glu Ile Asp Met Pro Tyr
Leu Leu Lys Tyr Gln Pro Met Met Gln Thr Ile Gly Gln Lys Tyr Cys
                    70
                                        75
Met Asp Pro Ala Val Ile Ala Gly Val Leu Ser Arg Lys Ser Pro Gly
Asp Lys Ile Leu Val Asn Met Gly Asp Arg Thr Ser Met Val Gln Asp
                                105
Pro Gly Ser Gln Ala Pro Thr Ser Trp Ile Ser Glu Ser Gln Val Ser
                            120
                                                125
Gln Thr Thr Glu Val Leu Thr Thr Arg Ile Lys Glu Ile Gln Arg Arg
                        135
                                            140
Phe Pro Thr Trp Thr Pro Asp Gln Tyr Leu Arg Gly Gly Leu Cys Ala
                    150
                                        155
Tyr Ser Gly Gly Ala Gly Tyr Val Arg Ser Ser Gln Asp Leu Ser Cys
                165
                                    170
Asp Phe Cys Asn Asp Val Leu Ala Arg Ala Lys Tyr Leu Lys Arg His
                                185
                                                    190
Gly Phe
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<211> 933 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(933) <221> misc_feature <222> (1)...(933) <223> n = A,T,C or G

<400> 115

<210> 115

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					ctc Leu								-	-	_	96
_			_		cgc Arg			_			_	-	_			144
					ccc Pro											192
-			_	_	agc Ser 70	-	_	-		-					•	240
_	-	-			ttc Phe	-	-				-	_		_	-	288
					gct Ala						-	_				336
-				_	gag Glu			-	-	-	_	-			-	384
-	-			_	agc Ser		-	_		-		-	_	-	-	432
					acc Thr 150								_			480
-	-			_	tct Ser			-						_	-	528
			_		gct Ala			-	-	-	-		-			576

					agg Arg						624
					cgc Arg						672
_	-				cga Arg 230			_	 -	 _	720
					gtc Val						768
					tgc Cys						816
					999 Gly						864
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	tgg Trp	-	_	-	cag Gln 310	tga *	•				933

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<213> Homo sapiens

<220>

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164

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													agc Ser			96
_		_		_						_	-		atc Ile	_		144
													gca Ala			192
-		-	_	_				_					aac Asn			240
							_		-		_		ttc Phe 95		•	288
													cac His		;	336
													atg Met	-	,	384
							-					 _	gac Asp	-	4	432

	He		tca Ser													480
			gag Glu													528
cga Arg	acc Thr	agt Ser	ctc Leu 180	atc Ile	att Ilė	ctt Leu	cag Gln	gga Gly 185	acc Thr	tgg Trp	ttc Phe	tgg Trp	cag Gln 190	att Ile	999 Gly	576
ttt Phe	gtg Val	ctg Leu 195	ttc Phe	cca Pro	cct Pro	ttt Phe	gga Gly 200	aca Thr	ccc Pro	gaa Glu	tgg Trp	gac Asp 205	cag Gln	aag Lys	gat Asp	624
			ctc Leu													672
			agc Ser													720
			atg Met										Gly			768
aag Lys	ctg Leu	aat Asn	tca Ser 260	gat Asp	gac Asp	act Thr	Tyr	cag G1n 265	acc Thr	gcc Ala	ctc Leu	ttg Leu	agt Ser 270	ggc Gly	tca Ser	816
gat Asp		gaa Glu 275	tga *													828
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<400> 118

Met Ala Asn Phe Lys Gly His Ala Leu Pro Gly Ser Phe Phe Leu Ile

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Ile	Gly	Leu	Cys 20	Trp	Ser	Val	Lys	Tyr 25	Pro	Leu	Lys	Tyr	Phe 30		His
Thr	Arg	Lys 35	Asn	Ser	Pro	Leu	His 40	Tyr	Tyr	Gln	Arg	Leu 45		Ile	Val
Glu	A1a 50	Ala	Пe	Arg	Thr	Leu 55		Ser	Val	Thr	Gly 60	_	Leu	Ala	Glu
G1n 65	Phe	Val	Pro	Asp	Gly 70		His	Leu	His	Leu 75		His	Glu	Asn	His 80
Trp	Пе	Lys	Leu	Met 85	Àsn	Trp	Gln	His	Ser 90	Thr	Met	Tyr	Leu	Phe 95	
Ala	Val	Ser	Gly 100	Ile	۷al	Asp	Met	Leu 105	Thr	Tyr	Leu	Val	Ser 110		Val
Pro	Leu	Gly 115	Val	Asp	Arg	Leu	Val 120	Met	Ala	Val	Ala	Val 125	Phe	Met	Glu
Gly	Phe 130	Leu	Phe	Tyr	Tyr	His 135	Val	His	Asn	Arg	Pro 140	Pro	Leu	Asp	Gln
His 145	Ile	His	Ser	Leu	Leu 150	Leu	Tyr	Ala	Leu	Phe 155	Gly	Gly	Cys	Val	Ser 160
Ile	Ser	Leu	Glu	Val 165	He	Phe	Arg	Asp	His 170	He	Val	Leu	Glu	Leu 175	Phe
Arg	Thr	Ser	Leu 180	Ile	Пе	Leu	Gln	Gly 185	Thr	Trp	Phe	Trp	Gln 190	Ile	Gly
		195					200	Thr			-	205		_	·
	210					215		Met			220				
A1a 225	Ala	Leu	Ser	Ile	Val 230	Ala	۷a٦	Asn	Tyr	Ser 235	Leu	Val	Tyr	Cys	Leu 240
Leu	Thr	Arg	Met	Lys 245	Arg	His	Gly	Arg	G1y 250	Glu	Пе	Пe	Gly	11e 255	Gln
			260	Asp	Asp	Thr	Tyr	G1n 265	Thr	Ala	Leu	Leu	Ser 270	Gly	Ser
Asp	Glu	G1u 275													
	<2 <2	210> 211> 212> 213>	867 Dna	sap	iens										
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1				5				10					15		06
-			-		cct Pro		_		-	_	_			_	96
					acc Thr										144
			-	_	 gcc Ala 55		_	-			-			_	192
					ttg Leu										240
	_	_			 tgg Trp	_	-		_		-	_	-	•	288
					aca Thr							-		_	336
_					cag Gln			_	•		-		•		384
					 cct Pro 135								-		432
	-		-		atg Met							_			480
					agt Ser										528

169

			165				170				175		
	gag Glu			_			•		_			_	576
	cca Pro 195												624
	cct Pro	-		_	-	 -					•	_	672
	cat His												720
	aat Asn											_	768
_	tat Tyr			_						_		_	816
	aga Arg 275					 		_	-	_	-	-	864
taa *													867

<210> 120

<211> 288

<212> PRT

<213> Homo sapiens

<400> 120

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<400> 121

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171

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	_			-						_		ctc Leu	_			96
	-						-		-		_	agt Ser 45		-	_	. 144
		_	_		_			-		-	-	ctt Leu	_	_	•	192
				-	_	_						gcc Ala				240
	_					-		-		-	-	tgc Cys			•	288
					-	_		-		-		cac His				336
			_		_							ccc Pro 125		-	_	384
												tcc Ser				432
												gat Asp				480
		•			_		•	•		•		ttc Phe				528
												ctg Leu				576

	180	185	190	
	ttc agg gcc cgc Phe Arg Ala Arg S			
	ttc acg gag cgg g Phe Thr Glu Arg / 215			
	cgg cca gcc ctg o Arg Pro Ala Leu b 230			
	ttc tcc atc ctg o Phe Ser Ile Leu I 245			
Leu Thr Leu	gat gga cac aac o Asp Gly His Asn L 260			
	cct ctg agg gag t Pro Leu Arg Glu 7 2		_	_
	cac atc cag gtc t His Ile Gln Val (295	Cys Thr Pro Trp		
	ctt cta ggg tcg g Leu Leu Gly Ser A 310	Ala Asp Leu Gly		
	ggc ctg gac ctg c Gly Leu Asp Leu F 325			
Cys Cys Leu	cct gtg tgt gct g Pro Val Cys Ala V 340			
	gaa gaa aat ggc c Glu Glu Asn Gly L			_

174

355 360 365 gca gct cag ctg cag atg ctt ttc tca aac ttt cct gat ctg cgg gca 1152 Ala Ala Gln Leu Gln Met Leu Phe Ser Asn Phe Pro Asp Leu Arg Ala 370 375 380 1158 agc taa Ser 385 <210> 124 <211> 385 <212> PRT <213> Homo sapiens <400> 124 Met Gln Tyr His Ala Leu Ser Leu Ala Met His Gly Phe Ser Val Thr Leu Leu Gly Phe Cys Asn Ser Lys Pro His Asp Glu Leu Leu Gln Asn Asn Arg Ile Gln Ile Val Gly Leu Thr Glu Leu Gln Ser Leu Ala Val Gly Pro Arg Val Phe Gln Tyr Gly Val Lys Val Val Leu Gln Ala Met 55 Tyr Leu Leu Trp Lys Leu Met Trp Arg Glu Pro Gly Ala Tyr Ile Phe 70 Leu Gln Asn Pro Pro Gly Leu Pro Ser Ile Ala Val Cys Trp Phe Val Gly Cys Leu Cys Gly Ser Lys Leu Val Ile Asp Trp His Asn Tyr Gly 105 Tyr Ser Ile Met Gly Leu Val His Gly Pro Asn His Pro Leu Val Leu 120 Leu Ala Lys Trp Tyr Glu Lys Phe Phe Gly Arg Leu Ser His Leu Asn 135 140 Leu Cys Val Thr Asn Ala Met Arg Glu Asp Leu Ala Asp Asn Trp His 155 145 150 Ile Arg Ala Val Thr Val Tyr Asp Lys Pro Ala Ser Phe Phe Lys Glu 165 170 Thr Pro Leu Asp Leu Gln His Arg Leu Phe Met Lys Leu Gly Ser Met 180 185 190 His Ser Pro Phe Arg Ala Arg Ser Glu Pro Glu Asp Pro Val Thr Glu 195 200 205 Arg Ser Ala Phe Thr Glu Arg Asp Ala Gly Ser Gly Leu Val Thr Arg

	210					215					220					
Leu 225		Glu	Arg	Pro	A1a 230	Leu		ı Val	Ser	Ser 235	Thr		Trp	Thr	G1u 240	
Asp	Glu	Asp	Phe	Ser 245	Ile		Leu	ı Ala	A1a 250	Leu		Lys	Phe	G1u 255	Gln	
Leu	Thr	Leu	Asp 260	Gly	His	Asn	Leu	Pro 265		Leu	۷a٦	Cys	Va1 270			
Gly	Lys	G1y 275	Pro	Leu	Arg	Glu	Tyr 280		Ser	Arg	Leu	Ile 285	His	Gln	Lys	
His	Phe 290	Gln	His	He	Gln	Va1 295		Thr	Pro	Trp	Leu 300	Glu	ΑÌa	Glu	Asp	
Tyr 305	Pro	Leu	Leu	Leu	Gly 310		Ala	Asp	Leu	Gly 315	Val	Cys	Leu	His	Thr 320	
Ser	Ser	Ser	Gly	Leu 325		Leu	Pro	Met	Lys 330	Val	۷a٦	Asp	Met	Phe 335	•	
Cys	Cys	Leu	Pro 340	Val	Cys	Ala	Val	Asn 345	Phe	Lys	Cys	Leu	His 350	Glu	Leu	
Val	Lys	His 355	Glu	Glu	Asn	Gly	Leu 360		Phe	Glu	Asp	Ser 365	Glu	Glu	Leu	
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Ser 385																
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	ggc Gly															96

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		Val										Leu			gtt Val	192
						Pro					Thr				caa G1n 80	240
												cgg Arg				288
												ggt Gly			tta Leu	336
			Gln									gtt Val 125				384
												ata Ile				432
												aca Thr				480
												gca Ala				528
												aca Thr				576
jag Nu	cag Gln	cac His	cag Gln	tta Leu	aac Asn	aag Lys	gaa Glu	agg Arg	gag Glu	ctt Leu	att Ile	gaa Glu	aga Arg	cta Leu	gag Glu	624

177

195		200	205	
-		Pro Leu Glu Lys	gta cga att gag Val Arg Ile Glu 220	
_			cta tgg ggt ggc Leu Trp Gly Gly	
	_	• • • •	cgg ctt acc tgg Arg Leu Thr Trp 255	0.0
Glu Tyr Ser T			tac ttc atc act Tyr Phe Ile Thr 270	
		•	atg aca cgc cag Met Thr Arg Gln 285	•
	•	Asp Arg Gln Tyr	tta cta ttt ttc Leu Leu Phe Phe 300	
			aaa tac aat caa Lys Tyr Asn Gln	
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<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(333)

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Gly	Gly	Gly	Gly 20	Gly	Gly	Ala	Gly	G1y 25	Cys	Gly	Ala	Leu	Thr 30		G1)
Cys	Phe	Pro 35	Gly	Leu	Gly	Val	Ser 40	Arg	His	Arg	Gln	G1n 45	Gln	His	His
Arg	Thr 50	Val	His	Gln	Arg	Ile 55	Ala	Ser	Trp	Gln	Asn 60	Leu	Gly	Ala	۷a٦
Tyr 65	Cys	Ser	Thr	Val	Va1 70	Pro	Ser	Asp	Asp	Va1 75	Thr	Val	۷a۱	Tyr	Glr 80
Asn	Gly	Leu	Pro	Va1 85	Пe	Ser	Val	Arg	Leu 90	Pro	Ser	Arg	Arg	G1u 95	Arg
Cys	Gln	Phe	Thr 100	Leu	Lys	Pro	Ile	Ser 105	Asp	Ser	Val	Gly	Val 110	Phe	Leu
Arg	Gln	Leu 115	Gln	Glu	Glu	Asp	Arg 120	Gly	Пe	Asp	Arg	Val 125	Ala	Пe	Tyr
Ser	Pro 130	Asp	Gly	Val	Arg	Val 135	Ala	Ala	Ser	Thr ·	Gly 140	Ile	Asp	Leu	Leu
145		Asp	·		150					155			•		160
		Pro		165					170					175	
		Val	180					185					190	•	
Glu	Gln	His 195	Gln	Leu	Asn	Lys	G1u 200	Arg	Glu	Leu	Ile	G1u 205	Arg	Leu	Glu
Asp	Leu 210	Lys	Glu	Gln	Leu	Ala 215	Pro	Leu	Glu	Lys	Val 220	Arg	Ile	Glu	He
Ser 225	Arg	Lys	Ala	Glu	Lys 230	Arg	Thr	Thr	Leu	Va1 235	Leu	Trp	Gly	Gly	Leu 240
		Met		245					250					255	•
		Ser	260					265					270		-
		A1a 275					280					285			
Tyr	Va1 290	Tyr	Pro	Glu	Ala	Arg 295	Asp	Arg	Gln	Tyr	Leu 300	Leu	Phe	Phe	His
305		Ala			310					315			Asn	Gln	Leu 320
Lys	Asp	Ala		A1a 325	Gln	Gln	Lys	Trp	Thr 330	Leu	Arg	Asp			

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	Met	Lys	Leu 115	His	His	Gly	Glu	Asn 120	_	Leu	Lys	Lys	Leu 125	Met	Cys	Cys	
											_	-			ggc Gly		432
															ccc Pro		480
						_			_		_	_	_	-	gtg Val 175	-	528
						_			-		_			_	gaa Glu	_	576
															aaa Lys		624
							-					-			ttt Phe		672
															gaa Glu		720
				Gly		Lys			Gln	-		-		-	cac His 255	-	768
					Lys										aag Lys		816
		Ser					Ser					Arg			agg Arg		864
(ctc	cac	ctt	cat	cag	aat	ggc	gtg	gaa	atg	ctc	atg	gaa	aat	gaa	gga	912

Leu	His 290	Leu	His	G1n	Asn	G1y 295	Val	Glu	Met	Leu	Met 300	Glu	Asn	Glu	Gly		
					aac Asn 310												960
					acg Thr											1	.008
					gag Glu												.056
				_	cat His		_		-				-		_	1	.104
					tcc Ser									_	-	1	152
-	gag Glu		-													1	164
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	Gln	Met	Leu 20		G1y	Leu	Gly	G]n 25		Val	Leu	Leu	Asn 30		Ser		
Leu	Thr	Pro	Lys	Tyr	Leu	G1y	Cys	Lys	Gln	Asp	Asn	Ser		Ser	Pro		

		35					40					45			
Lys	Pro 50	Ser	Ser	Val	Phe	Arg 55	Asn	Gly	Phe	Ser	G1y 60	Ile	Lys	Lys	Pro
Trp 65	His	Arg	Cys	His	Val 70	Cys	Asn	His	His	Phe 75	Gln	Phe	Lys	Gln	His 80
Leu	Arg	Asp	His	Met 85	Asn	Thr	His	Thr	Asn 90	Arg	Arg	Pro	Tyr	Ser 95	Cys
Arg	Ile	Cys	Arg 100	Lys	Ser	Tyr	Val	Arg 105	Pro	Gly	Ser	Leu	Ser 110	Thr	His
Met	Lys	Leu 115	His	His	Gly	Glu	Asn 120	Arg	Leu	Lys	Lys	Leu 125	Met	Cys	Cys
Glu	Phe 130	Cys	Ala	Lys	Val	Phe 135	Gly	His	Пe	Arg	Val 140	Tyr	Phe	Gly	His
Leu 145	Lys	Glu	Val	His	Arg 150	Val	Val	Пe	Ser	Thr 155	Glu	Pro	Ala	Pro	Ser 160
Glu	Leu	Gln	Pro	Gly 165	Asp	Ile	Pro	L <u>y</u> s	Asn 170	Arg	Asp	Met	Ser	Val 175	Arg
			180		Leu		_	185					190		
Asp	Phe	Leu 195	Leu	Asn	Gln	Ala	Asp 200	Glu	Val	Lys	Leu	G1n 205	Ile	Lys	Cys
	210				Thr	215					220		•		
225					Gly 230					235					240
				245	Lys				250					255	
			260		Arg			265		-	-		270	•	
		275			Glu		280		•		_	285	·		
	290				Asn	295					300				·
305					Asn 310					315					320
				325	Thr				330					335	
Cys	Leu	Leu	Cys 340	Ala	Glu	Met	Leu	G1y 345	Arg	Lys	Glu	Asp	Leu 350	Leu	His
His	Trp	Lys 355	His	Gln	His	Asn	Cys 360	Glu	Asp	Pro	Ser	Lys 365	Leu	Trp	Ala
Ile	Leu 370	Asn	Thr	Val	Ser	Asn 375	Gln	Gly	Val	Ile	G1u 380	Leu	Ser	Ser	Glu
Δla	Glu	Lvs													

183

385

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						aca Thr 120									384
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						gaa G1u			-		_				480
						ctg Leu	-		-				-		528
		-			_	aac Asn		_			-				576
_					_	gtc Val 200	_		_	_			_	_	624
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					-	tat Tyr	-	-	-	_	-			-	720
						999 Gly									768
	Ser					gct Ala									816
Tyr						gtc Val 280									864

	Phe						tat Tyr		Thr			912
Leu		_	-		-		cct Pro 315	Gln				960
							gga Gly					1008
							tat Tyr					1056
					-	_	tct Ser	-		-		1104
							gga Gly					1152
							cga Arg 395				ttt Phe 400	1200
							gtc Val					1248
_	_	_					agg Arg					1296
Pro				Thr			gct Ala					1344
			Lys				gtt Val					1392

	His				Asn			Gly			aaa Lys 480	1440	
				Thr					gat Asp			1488	
									cat His 510			1536	
									aaa Lys			1584	
									gta Val			1632	
									gga Gly			1680	•
									gga Gly			1728	
									cca Pro 590			1776	
									tta Leu			1824	
Ser									gat Asp			1872	
gaa Glu 625			Leu				Tyr		agt Ser	Asn		1920	

			att Ile													1968
-		-	gaa G1u 660	-												2016
cct Pro	tga *									٠						2022
		٠														
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		220>														
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			Xaa			nino	Acid	d								
	_	100~	120													
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1 Ala	Lys Cys	Lys Pro Gln	Asp	5 Met	Ala	Thr	Cys Cys	Gly 25	10 Asn	Val	Leu	Phe Glu	G1u 30	15 Gly	Arg	
1 Ala Thr	Lys Cys Val Glu	Lys Pro Gln 35	Asp His 20	5 Met Gly	Ala Lys	Thr Leu Asn	Cys Cys 40	Gly 25 Cys	10 Asn Thr	Val Gly	Leu Val Gln	Phe Glu 45	Glu 30 Thr	15 Gly Glu	Arg Asp	
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1 Ala Thr Asp Val 65	Lys Cys Val Glu 50 Pro	Lys Pro Gln 35 Asp	Asp His 20 Leu Thr	5 Met Gly Glu Pro Lys	Ala Lys Ser Thr 70	Thr Leu Asn 55 Leu	Cys Cys 40 Ser His	Gly 25 Cys Ser Asp	10 Asn Thr Val Pro	Val Gly Glu Asp 75	Leu Val Gln 60 Leu	Phe Glu 45 Ala Tyr	Glu 30 Thr Ser	15 Gly Glu Val Glu Tyr	Arg Asp Glu Ile 80	
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1 Ala Thr Asp Val 65 Val Asp	Lys Cys Val Glu 50 Pro Lys Tyr	Lys Pro Gln 35 Asp Asp Tyr 115	Asp His 20 Leu Thr Gly Thr Gly 100	5 Met Gly Glu Pro Lys 85 His	Ala Lys Ser Thr 70 Ser Ile Gln	Thr Leu Asn 55 Leu Val Pro Arg	Cys 40 Ser His Pro Thr 120	Gly 25 Cys Ser Asp Glu Pro 105 Lys	10 Asn Thr Val Pro Tyr 90 Phe Ile	Val Gly Glu Asp 75 Ser Lys Ala	Leu Val Gln 60 Leu Glu Glu	Phe Glu 45 Ala Tyr Val Pro Asp 125	Glu 30 Thr Ser Ile Ala Ile 110 Ile	15 Gly Glu Val Glu Tyr 95 Leu Glu	Arg Asp Glu Ile 80 Pro Glu Arg	

Ser	Lys	Phe	Glu	Ser 165	Gly	Asn	Leu	Arg	Xaa 170	Val	Ile	Gln	Ile	Arg 175	Lys
Asn	Glu	Tyr	Asp 180	Leu	Ile	Leu	Asn	Ser 185	Asp	Пe	Asn	Ser	Asn 190	His	Tyr
His	Gl'n	Trp 195	Phe	Tyr	Phe	Glu	Val 200	Ser	Gly	Met	Arg	Pro 205	Gly	Val	Ala
Tyr	Arg 210	Phe	Asn	Пe	He	Asn 215	Cys	Glu	Lys	Ser	Asn 220	Ser	G1n	Phe	Asn
225	•				230					235	Glu				240
		•		245			`		250		Cys			255	
			260					265	_	-	Gln		270	-	
•	Ť	275					280				His	285	•	·	
·	290			-		295				Ť	Ser 300				
305			•		310					315	Gln			,	320
Arg	Lys	Asp	Val	Leu 325	Cys	Glu	Thr	Leu	Ser 330	Gly	Asn	Ser	Cys	Pro 335	Leu
Val	Thr	Пе	Thr 340	Ala	Met	Pro	Glu	Ser 345	Asn	Tyr	Tyr	Glu	His 350	He	Cys
His	Phe	Arg 355	Asn	Arg	Pro	Tyr	Va1 360	Phe	Leu	Ser	Ala	Arg 365	Val	His	Pro
G1y	G1u 370	Thr	Asn	Ala	Ser	Trp 375	Val	Met	Lys	Gly	Thr 380	Leu	Glu	Tyr	Leu
Met 385	Ser	Asn	Asn	Pro	Thr 390	Ala	Gln	Ser	Leu	Arg 395	Glu	Ser	Tyr	Ile	Phe 400
Lys	Пe	Val	Pro	Met 405	Leu	Asn	Pro	Asp	Gly 410	Val	Ile	Asn	Gly	Asn 415	His
Arg	Cys	Ser	Leu 420	Ser	Gly	Glu	Asp	Leu 425	Asn	Arg	Gln	Trp	G1n 430	Ser	Pro
Ser	Pro	Asp 435	Leu	His	Pro	Thr	Ile 440	Tyr	His	Ala	Lys	G1y 445	Leu	Leu	Gln
Tyr	Leu 450	Ala	Ala	Val	Lys	Arg 455	Leu	Pro	Leu	Val	Tyr 460	Cys	Asp	Tyr	His
G1y 465	His	Ser	Arg	Lys	Lys 470	Asn	Val	Phe	Met	Tyr 475	Gly	Cys	Ser	Пe	Lys 480
Glu	Thr	Val	Trp	His 485	Thr	Asn	Asp	Asn	A1a 490	Thr	Ser	Cys	Asp	Va1 495	۷a۱
Glu	Asp	Thr	G1y 500	Tyr	Arg	Thr	Leu	Pro 505	Lys	Пe	Leu	Ser	His 510	Ile	Ala

Pro	Ala	Phe 515	Cys	Met	Ser	Ser	Cys 520	Ser	Phe	Val	Val	G1u 525	Lys	Ser	Lys	
Glu	Ser 530		Ala	Arg	Val	Va1 535		Trp	Arg	Glu	Ile 540		Val	Gln	Arg	•
Ser 545	Tyr	Thr	Met	Glu	Ser 550	Thr	Leu	Cys	Gly	Cys 555	Asp	Gln	Gly	Lys	Tyr 560	
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Phe	Cys	Val	Gly 580	Leu	Leu	Arg	Leu	Lys 585	Arg	Leu	Thr	Ser	Pro 590	Leu	Glu	
Tyr	Asn	Leu 595	Pro	Ser	Ser	Leu	Leu 600	Asp	Phe	Glu	Asn	Asp 605	Leu	Пe	Glu	
Ser	Ser 610	Cys	Lys	Val	Thr	Ser 615	Pro	Thr	Thr	Tyr	Val 620	Leu	Asp	Glu	Asp	
G1u 625	Pro	Arg	Phe	Leu	G1u 630	Glu	Val	Asp	Tyr	Ser 635	Ala	Glu	Ser	Asn	Asp 640	
Glu	Leu	Asp	Пe	G1u 645	Leu	Ala	Glu	Asn	Va1 650	Gly	Asp	Tyr	Glu	Pro 655	Ser	
Ala	Gln	Glu	G1u 660	Val	Leu	Ser	Asp	Ser 665	Glu	Leu	Ser	Arg	Thr 670	Tyr	Leu	
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					gga Gly		-				_	_				144

			ggt Gly										-			192
	Gly	_	gtt Val			_		_		-	_			•		240
	_		gaa Glu								_	-	_			288
_			gcc Ala 100							_			-	-		336
		_	ctc Leu		_			Gly				tga *				375
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Asp	Tyr	Ser	Leu 20	Ala	Val	Ala	Phe	Leu 25	Thr	Ile	Ser	Thr	Thr 30	Leu	Gly	
Gly	Phe	Cys 35	Ser	Ser	Gly	Phe	Ser 40		Asn	His	Leu	Asp 45		Ala	Pro	
Ser	Tur		Glv	110	Lou	ا بو ا		م۱۱	Thr	۸cn	Thr		α۱۸	Thr	Πρ	
		Alu	uıy	116	Leu		uly	110		ASII		riic	Aia	1111	110	
	50		Val		Pro	55				Ser	60				Asn	
65	50 Gly	Met		Gly Trp	Pro 70	55 Val	Пe	Ala	Lys Tyr	Ser 75	60 Leu	Thr	Pro	Asp Ile	Asn 80	
65 Thr	50 Gly Val	Met Gly	Val	Gly Trp 85	Pro 70 Gln	55 Val Thr	Ile Val	Ala Phe	Lys Tyr 90	Ser 75 Ile	60 Leu Ala	Thr Ala	Pro Ala	Asp Ile 95	Asn 80 Asn	

WO 01/29221

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PCT/US00/29052

Arg	Pro	Pro 115	Arg	Cys	Ser	His	Cys 120	Ser	Val	Cys	Asp	Asn 125	Cys	Val	Glu	
					tgc Cys											432
		_			ttc Phe 150						_		-			480
_					ttt Phe					_						528
-				-	cgc Arg	_	-	-				-		-		576
-					atc Ile		_	_			_					624
_	_		-		gga Gly	_				-	_	-	_			672
					aac Asn 230							-				720
		Val	Leu		agt Ser		Pro		Pro	Arg						768
-		-	_		att Ile	_		_					-		-	816
					ata Ile											864
gga	gag	ctg	agg	aga	aca	aag	tct	aag	gga	agc	ctg	gag	ata	aca	gag	912

WO 01/29221

PCT/US00/29052

G1y	G1u 290	Leu	Arg	Arg	Thr	Lys 295	Ser	Lys	Gly	Ser	Leu 300	Glu	Ile	Thr	Glu	
•	_		-	_	_	gaa Glu						-		-	_	960
						cga Arg										1008
_	-					aag Lys										1056
						agt Ser										1104
			-	-	-	ttg Leu 375	_	-		_	-	_				1152
						agc Ser										1200
_	_	-			-	ttc Phe										1248
		-				agt Ser										1296
	•			~ ~		gag Glu	-		-	-				-		1344
						tcc Ser 455										1392
aat	gga	agc	cta	tct	tat	gac	agc	ttg	ctc	aca	cct	tca	gac	agc	cct	1440

194

Asn Gly Ser Leu Ser Tyr Asp Ser Leu Leu Thr Pro Ser Asp Ser Pro 465 470 475 480 gat ttt gag tca gtg cag gca ggg ctg agc cag acc cac ctt tag 1485 Asp Phe Glu Ser Val Gln Ala Gly Leu Ser Gln Thr His Leu * 490 485 <210> 134 <211> 494 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(494) <223> Xaa = Any Amino Acid <400> 134 Met Pro Ala Glu Ser Gly Lys Arg Phe Lys Pro Ser Lys Tyr 'Val Pro 1 5 Val Ser Ala Ala Ala Ile Phe Leu Val Gly Ala Thr Thr Leu Phe Phe Ala Phe Thr Cys Pro Gly Leu Ser Leu Tyr Val Ser Pro Ala Val Pro Ile Tyr Asn Ala Ile Met Phe Leu Phe Val Leu Ala Asn Phe Ser Met 55 60 Ala Thr Phe Met Asp Pro Gly Ile Phe Pro Arg Ala Glu Glu Asp Glu 70 65 Asp Lys Glu Asp Asp Phe Arg Ala Pro Leu Tyr Lys Thr Val Glu Ile 90 Lys Gly Ile Gln Val Arg Met Lys Trp Cys Ala Thr Cys Arg Phe Tyr 105 Arg Pro Pro Arg Cys Ser His. Cys Ser Val Cys Asp Asn Cys Val Glu 120 125 Glu Phe Asp His His Cys Pro Trp Val Asn Asn Cys Ile Gly Arg Arg 135 140 Asn Tyr Arg Tyr Phe Phe Leu Phe Leu Leu Ser Leu Thr Ala His Ile 150 155 Met Gly Val Phe Gly Phe Gly Leu Leu Tyr Val Leu Tyr His Ile Glu 165 170 175 Glu Leu Ser Gly Val Arg Thr Ala Val Thr Met Ala Val Met Cys Val 180 185 190 Ala Gly Leu Phe Phe Ile Pro Val Ala Gly Leu Thr Gly Phe His Val

		195					200					205			
	210			Arg		215					220				Ī
Phe 225		Gly	Gly	Val	Asn 230	Pro	Phe	Thr	Asn	G1y 235	Cys	Cys	Asn	Asn	Val 240
Ser	Arg	Val	Leu	Cys 245	Ser	Ser	Pro	Ala	Pro 250	Arg	Tyr	Leu	Gly	Arg 255	Pro
Lys	Lys	Glu	Lys 260	Thr	Пe	Val	Пe	Arg 265		Pro	Phe	Leu	Arg 270	Pro	Glu
Val	Ser	Asp 275	Gly	Gln	Пe	Thr	Va1 280	Lys	He	Met	Asp	Asn 285	Gly	Ile	Gln
Gly	G1u 290	Leu	Arg	Arg	Thr	Lys 295	Ser	Lys	Gly	Ser	Leu 300	Glu	Пe	Thr	G1u
305				Asp	310					315		-		·	320
Ser	Arg	Tyr	Thr	Gly 325	Leu	Arg	Thr	His	Leu 330	Gly	Leu	Ala	Thr	Asn 335	Glu
Asp	Ser	Ser	Leu 340	Leu	Ala	Lys	Asp	Ser 345	Pro	Pro	Thr	Pro	Thr 350	Met	Tyr
Lys	Tyr	Arg 355	Pro	Gly	Tyr	Ser	Ser 360	Ser	Ser	Thr	Ser	A1a 365	Ala	Met	Pro
His	Ser 370	Ser	Ser	Ala	Lys	Leu 375	Ser	Arg	Gly	Asp	Ser 380	Leu	Lys	Glu	Pro
Thr 385	Ser	Ile	Ala	Glu	Ser 390	Ser	Arg	His	Pro	Ser 395	Tyr	Arg	Ser	G1u	Pro 400
Ser	Ĺeu	Glu	Pro	G1u 405	Ser	Phe	Arg	Ser	Pro 410	Thr	Phe	Gly	Lys	Ser 415	Phe
			420	Leu				425					430		
Xaa	Gln	G1y 435	Thr	Gly	Phe	Glu	Leu 440	Gly	Gln	Leu	Gln	Ser 445	He	Arg	Ser
Glu	Gly 450	Thr	Thr	Ser	Thr	Ser 455	Tyr	Lys	Ser	Leu	Ala 460	Asn	Gln	Thr	Arg
Asn 465	Gly	Ser	Leu	Ser	Tyr 470	Asp	Ser	Leu	Leu	Thr 475	Pro	Ser	Asp	Ser	Pro 480
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 40
 45

 Val Gly Trp Gln Glu Val Ser Ala Ala Phe Asp Pro Asn Ser Phe Tyr 50
 55
 60

Asn Leu Cys Leu Thr Ser Leu Ser Ser Gln Gln Gln Arg Thr Leu

65 Asp					70					75			•		80	
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						aaa Lys 55									_	192
				_	-	gcg Ala						_				240
					-	att Ile		_	_	_	-		-	-	tct Ser	288
						ttc Phe										336
						ctg Leu										384

		115					120					125					
			tat Tyr										-		_		432
			gag Glu											-	_		480
		_	ggc Gly		_		-		_	_		_			_	,	528
			ctg Leu 180														552
	<2 <2			o sap	oiens	5											
Met 1		100> G1n	138 Arg	Leu 5	Ala	Glu	Phe	Arg	Ala 10	Ala	Arg	Lys	Arg	Ala 15	Gly		
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Glu	Lys	A1 a 35	Glu	Ala	Ala	Ala	Thr 40	Leu	Lys	Ala	Ala	Pro 45		Trp	Leu		
Lys	Arg 50	Phe	Leu	Val	Trp	Lys 55	Pro	Arg	Pro	Ala	Ser 60	Ala	Arg	Ala	Gln		
Pro 55	Gly	Leu	Val		G1u 70	Ala	Ala	Gln	Pro	G1n 75	Gly	Ser	Thr	Ser	Glu 80		
Thr	Pro	Trp	Asn	Thr 85	Ala	Ile	Pro	Leu	Pro 90	Ser	Cys	Trp	Asp	G1n 95	Ser		
Phe	Leu	Thr	Asn 100		Thr	Phe	Leu	Lys 105	Val	Leu	Leu	Trp	Leu 110		Leu		
_eu	Gly	Leu 115	Phe	Val	Glu		G1u 120		Gly	Leu	Ala	Tyr 125		Va1	Leu		
Ser	Leu 130		Tyr	Trp	Met			Gly	Thr	Arg	Gly 140		Glu	Glu	Lys		
_ys		Gly	Glu	Lys	Ser		Tyr	Ser	Val	Phe		Pro	Gly	Cys	Glu		

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			ctc Leu 20									_		_		96
-	_	-	ctc Leu			-	-				_				_	144
			aga Arg													192
	_		gtc Val	-		-	-	-	_			-	-			240
_	-		gaa Glu									_				288
-	-		aaa Lys 100		-	-	_		-			_	_	-	_	336

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						cct Pro 135								_		432
		-				aac Asn	_			_			-			480
						gct Ala	-		_			-	-		-	528
			_			ctg Leu	_		-			_		-	~ ~	576
						ccg Pro	-		-							624
-	_		_	-	_	aga Arg 215		-	-						•	672
						ctg Leu			_				-	-	•	720
						aac Asn									cag Gln	768
			-	_	_	tca Ser		_		-	_	-		_	_	816
	Gly					gaa Glu										864

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Thr Arg Ser Arg Asp Arg Ser Leu Leu Pro Ser Asp Asp Glu Leu Lys

			260					265					270			
		275	•				Asp 280				· ·	285			Phe	
Ser	Asn 290	Arg	Phe	Pro	Arg	Trp 295	Val	Pro	Trp	Met	Val 300	Lys	Ser	Glu		
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							tca Ser									240
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203

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-				aat Asn 150	-						_		-		480
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	-	_	-	 att Ile			-	-		-			_		576
	_		_	aaa Lys		-				_	_	_			624
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						gct Ala				-			-	_	_	288
						gtg Val										336
						999 Gly										384
Leu	ccc Pro 130	ctg Leu	999 Gly	ccg Pro	cac His	ctc Leu 135	cag G1n	gac Asp	ctg Leu	ttc Phe	acc Thr 140	ggc Gly	cac His	cgg Arg	ttc Phe	432
						ggc Gly										480
						acc Thr										528

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gat Asp	999 Gly	ttg Leu	ttg Leu 180	ggc Gly	tcc Ser	ccg Pro	gcc Ala	cgg Arg 185	Leu	gcc Ala	tcc Ser	cag Gln	ctg Leu 190	Leu	ggc Gly	576
gat Asp	gag Glu	ctg Leu 195	ctt Leu	ctc Leu	gcc Ala	aaa Lys	ctg Leu 200	ccc Pro	ccc Pro	agc Ser	cgg Arg	gaa G1u 205	agt Ser	gcc Ala	ttc Phe	624
			ggc Gly													672
ctc Leu 225	aca Thr	gag Glu	tcc Ser	tgc Cys	ctt Leu 230	tcc Ser	ccc Pro	gcg Ala	gag Glu	gag Glu 235	gag Glu	cca Pro	gcc Ala	ccc Pro	tgc Cys 240	720
			cag Gln													768
cag Gln	cgg Arg	caa Gln	gcc Ala 260	tct Ser	gac Asp	ctg Leu	gcc Ala	tct Ser 265	tct Ser	999 Gly	gtg Val	gtg Val	tcc Ser 270	tta Leu	gat Asp	816
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Leu	Ala	Arg	Ser 20	Ser	Leu	His	Gly	11e 25	Ser	Gln	Val	Val	Lys 30	Asp	His
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	50				Ser	55					60				
65					Tyr 70					75					80
				85	Val				90					95	_
			100		Ser			105					110	•	
		115			Ala		120				·	125		_	
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145					Gln 150					155			•		160
				165	Asp				170		٠			175	
			180		Ser			185					190		•
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225					Leu 230					235					240
				245	Leu Asp				250					255	
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		-		ctt Leu 85	-			-					-	-		288
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					gcc Ala					-	-			-	720
					cgc Arg `										768
					atc Ile				-						816
					gcc Ala		_						-		864
					ggc Gly 295			-		-		-			912
-				_	ccc Pro	_		_	_			-			960
	_	-			ttc Phe	-	Leu					_			1008
					tcc Ser	Phe									1056

	tgt Cys		Leu										Arg			1104
	cct Pro 370	Glu										Phe		_		1152
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•	Gly	Leu	G1u 20	-	Ser	Arg		Arg 25		Lys	Pro	Pro	G1y 30		Ala	
Cys	Ser	Asn 35		Ser	Phe				Gln	Leu	Asp	Phe 45		Gln	Val	
Tyr	Phe 50		Ala	Leu				Trp	Leu		A1a 60		Tyr	Leu	Tyr	

Lys 65	Leu	Tyr	Gln	His	Tyr 70	Tyr	Phe	Leu	Glu	G1y 75	Gln	Пe	Ala	Ile	Leu 80
Tyr	Val	Cys	Gly	Leu 85	Ala	Ser	Thr	Val	Leu 90	Phe	Gly	Leu	۷a٦	A1 a 95	Ser
Ser	Leu	Val	Asp 100	-	Leu	Gly	Arg	Lys 105	Asn	Ser	Cys	Val	Leu 110		Ser
Leu	Thr	Tyr 115		Leu	Cys	Cys	Leu 120		Lys	Leu	Ser	G1n 125	Asp	Tyr	Phe
	130			_		135		•	_		140				Leu
145					150					155					His 160
				165	Trp				170					175	
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		195			Leu		200					205			
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225					Arg 230					235					240
				245	Asp				250					255	
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		275			Gly		280		_			285			
	290				Leu	295					300				
305					Gln 310					315					320
				325	Leu				330					335	•
			340		Glu			345					350		
		355			Phe		360					365			
	370					375					380				
385					Cys 390					395					400
Arg	Lys	Thr		Thr 405	Arg	Asn	Met		Ser 410	Пe	Cys	Ser	Ala	Val 415	Met

212

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					ctc Leu									-	_	336
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1 Leu Ala Leu Cys 65	Ala Tyr Leu Val 50 Ser	Gly Gln Ala 35 Leu Ser	Pro Ala 20 Arg Arg Leu	·5 Ala Phe Arg Leu Gìn	His Tyr Asp	Cys Cys Pro 55 Pro	Val Tyr 40 Ser Gly	Leu 25 Thr Val Leu	10 Ala Glu Lys Thr	Gln Arg Arg Cys 75	Asp Thr Thr 60 Thr	Pro Ile 45 Leu Gln	Glu 30 Ala Cys Arg	15 Asn Lys Arg Gln Cys	Gln Xaa Gly Arg 80	
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1 Leu Ala Leu Cys 65 Arg Arg	Ala Tyr Leu Val 50 Ser Cys Ser Pro	Gly Gln Ala 35 Leu Ser Arg Gln Glu 115	Pro Ala 20 Arg Arg Leu Gly Arg 100 Ala	Phe Arg Leu Gîn 85 Phe Gîn	His Tyr Asp Val 70 Arg Leu	Cys Cys Pro 55 Pro Trp Asn Gly	Val Tyr 40 Ser Gly Thr Asp Ser 120	Leu 25 Thr Val Leu Val Pro 105 Gln	10 Ala Glu Lys Thr Gln 90 Gly	Gln Arg Arg Cys 75 Thr His	Asp Thr Thr 60 Thr Cys Leu Ser	Pro Ile 45 Leu Gln Leu Leu Lys 125	Glu 30 Ala Cys Arg Thr Trp 110 Pro	15 Asn Lys Arg Gln Cys 95 Gly Leu	Gln Xaa Gly Arg 80 Gln Asp	

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			act Thr													96	
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			acc Thr													240	
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(cac	tga														390	

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96

215

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<212> PRT

<213> Homo sapiens

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Ala Ala Val Ala Val Leu Val Ala Ser Val Tyr Pro Arg Lys Pro 35 40 45

Gln Ala Val Glu Arg His Val Leu Pro Ile Leu Trp His Phe Leu Asn 50 55 60

Thr Ala Thr Arg Asn Gly Thr Leu Pro Gly Pro Ser Gly Asn Ile Arg 65 70 75 80

Gly Val Val Cys Arg Leu Ser Arg Ser Leu Gln Glu His His Gly Leu 85 90 95

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His

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									cac His						ggc Gly	192
									ctg Leu							240
									tgt Cys 90							288
									cct Pro							336
									999 Gly							384
									cca Pro							432
	Val	Gly	Ala	Pro	Ala	Val	Gln	Ser	atc Ile	Leu	Val	Ala	Gly			480
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Gly Val Val Phe Val Leu Arg Tyr Gln Arg Lys Glu Pro Pro Asp Ser
                            40
Ala Thr Asp Pro Thr Ser Pro Gln Pro His Asn Trp Val Trp Leu Gly
Thr Asp Gln Glu Glu Leu Ser Arg Gln Leu Asp Arg Gln Ser Pro Gly
Pro Pro Lys Gly Glu Gly Ser Cys Pro Cys Glu Ser Gly Gly Gly
Glu Ala Pro Thr Leu Ala Pro Gly Pro Pro Gly Gly Thr Thr Ser Ser
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Ser Ser Thr Leu Ala Arg Lys Glu Ala Gly Gly Arg Arg Lys Arg Val
                            120
Glu Phe Val Thr Phe Ala Pro Ala Pro Pro Ala Gln Ser Pro Glu Glu
                        135
Pro Val Gly Ala Pro Ala Val Gln Ser Ile Leu Val Ala Gly Glu Glu
                    150
                                        155
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_	-	-	gat Asp							-	_		240
			gat Asp										288
-			gag Glu 100						-	_			336
-			ctg Leu	 _			_	_	-				384
_		-	agt Ser						-	-			432
			cag Gln										480
			atg Met		_	_	_		-				528
			aac Asn 180										576

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					cac His						-	_	-		-	672
	-		_	-	tcc Ser 230			_	_				-		-	720
	aac Asn	-	tcg Ser	tga *												735
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1 Gly Gly Leu Gln 65 Gly Gln Leu	Ala Gly Ala Glu 50 Glu Arg Arg Asn	Thr Arg Arg 35 Gln Asp Leu Pro Leu 115	Gly 20 Val Glu Asp Asp Glu 100 Leu	5 Ile Val Leu Val Cys 85 Glu Gly	Gly Ile Pro Lys 70 Val	Ala Cys Gly 55 Thr Val Ser	Asp 40 Ala Leu Asn Ala Thr 120	Ile 25 Lys Val Val Asn Gln 105 Leu	10 Val Asp Phe Ser Ala 90 Gly Thr	Arg Glu Ile Glu 75 Gly Phe Lys	Ala Ser Leu 60 Thr His Arg	Phe Gly 45 Cys Ile His Gln Ala 125	Val 30 Gly Asp Arg Pro Leu 110 Leu	15 Asn Arg Val Arg Pro 95 Leu Pro	Ser Ala Thr Phe 80 Pro Glu Tyr	

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V-1	۸~	W-1	۸	165		C	D	C1	170	77-	T	т.	.	175		
Vai	Arg	vai	180	Lys	11e	Ser	Pro	185	Asn	Пе	irp	Inr	Pro 190	Leu	Irp	
Glu	Glu	Leu 195		Ala	Leu	Met	Pro 200	Asp	Pro	Arg	Ala	Thr 205	Ile	Arg	Glu	
Gly	Met 210		Pro	Ser	His	Trp 215	Ala	Ala	Trp	Ala	Ser 220	Pro	Leu	Arg	Ser	
G1y 225	Leu	Arg	G1n	Cys	Ser 230	Trp	Pro	Pro	Lys	Pro 235	Thr	Ser	Ala	Arg	Ala 240	
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Met	<'a	222> 223> 400> ctg	(1) n = 155 gca	A,T,	975) .C or ggc	G ctt			His					Āsp		48
	<2 <2 atg	222> 223> 400> ctg	(1) n = 155 gca	 A,T,	975) .C or ggc	G ctt										48
Met 1	<2 <2 atg	222> 223> 400> ctg Leu	(1), n = 155 gca Ala	A.T.	975) .C on ggc Gly	°G ctt Leu	Leu	Leu	His 10	Xaa	Xaa	Xaa	Xaa	Asp 15	Trp	48 96
Met 1 aca	<pre> </pre> <pre> </pre> <pre> atg Met</pre>	222> 223> 400> ctg Leu	(1). n = 155 gca Ala gag Glu	A.T. cag Gln 5	975) .C on ggc Gly atg	ctt Leu ggc	Leu ctg	Leu ggc Gly	His 10 ccc	Xaa cct	Xaa gag	Xaa ctg	Xaa tca Ser	Asp 15 999	Trp	
Met 1 aca	<2 <2 atg Met	222> 223> 400> ctg Leu	(1) n = 155 gca Ala	A.T. cag Gln 5	975) .C on ggc Gly atg	ctt Leu ggc	Leu ctg	Leu ggc	His 10 ccc	Xaa cct	Xaa gag	Xaa ctg	Xaa tca	Asp 15 999	Trp	
Met 1 aca Thr	<pre> <2</pre>	222> 223> 400> ctg Leu gcc Ala	(1). n = 155 gca Ala gag Glu 20 agc	cag Gln 5 ggc Gly	975) C on ggc Gly atg Met	ctt Leu ggc Gly	ctg Leu ggg	ggc Gly 25	His 10 ccc Pro	Xaa cct Pro	Xaa gag Glu tgg	Xaa ctg Leu	tca Ser 30	Asp 15 999 Gly	Trp tca Ser	
Met 1 aca Thr	<pre><2 <2 atg Met tgg Trp</pre>	222> 223> 400> ctg Leu gcc Ala	(1). n = 155 gca Ala gag Glu 20 agc	cag Gln 5 ggc Gly	975) C on ggc Gly atg Met	ctt Leu ggc Gly	ctg Leu ggg Gly	ggc Gly 25	His 10 ccc Pro	Xaa cct Pro	Xaa gag Glu tgg	Xaa ctg Leu atg Met	tca Ser 30	Asp 15 999 Gly	Trp tca Ser	96
Met 1 aca Thr	<pre> <2</pre>	222> 223> 400> ctg Leu gcc Ala	(1). n = 155 gca Ala gag Glu 20 agc	cag Gln 5 ggc Gly	975) C on ggc Gly atg Met	ctt Leu ggc Gly	ctg Leu ggg	ggc Gly 25	His 10 ccc Pro	Xaa cct Pro	Xaa gag Glu tgg	Xaa ctg Leu	tca Ser 30	Asp 15 999 Gly	Trp tca Ser	96
Met 1 aca Thr gcc Ala	atg Met tgg Trp tct Ser	222> 223> 400> ctg Leu gcc Ala ccc Pro 35	(1) n = 155 gca Ala gag Glu 20 agc Ser	cag Gln 5 ggc Gly	ggc Gly atg Met tac Tyr	ctt Leu ggc Gly cat His	ctg Leu ggg Gly 40 ctg	ggc Gly 25 cct Pro	His 10 ccc Pro gcc Ala cag	Cct Pro cgc Arg	Xaa gag Glu tgg Trp	Ctg Leu atg Met 45	tca Ser 30 ccc Pro	Asp 15 ggg Gly cca Pro	Trp tca Ser cgc Arg	96
Met 1 aca Thr gcc Ala	<pre> <2</pre>	222> 223> 400> ctg Leu gcc Ala ccc Pro 35	(1) n = 155 gca Ala gag Glu 20 agc Ser	cag Gln 5 ggc Gly	ggc Gly atg Met tac Tyr	ctt Leu ggc Gly cat His	ctg Leu ggg Gly 40 ctg	ggc Gly 25 cct Pro	His 10 ccc Pro gcc Ala cag	Cct Pro cgc Arg	Xaa gag Glu tgg Trp cgc Arg	Ctg Leu atg Met 45	tca Ser 30 ccc Pro	Asp 15 ggg Gly cca Pro	Trp tca Ser cgc Arg	96 144
Met 1 aca Thr gcc Ala	atg Met tgg Trp tct Ser	222> 223> 400> ctg Leu gcc Ala ccc Pro 35	(1) n = 155 gca Ala gag Glu 20 agc Ser	cag Gln 5 ggc Gly	ggc Gly atg Met tac Tyr	ctt Leu ggc Gly cat His	ctg Leu ggg Gly 40 ctg	ggc Gly 25 cct Pro	His 10 ccc Pro gcc Ala cag	Cct Pro cgc Arg	Xaa gag Glu tgg Trp	Ctg Leu atg Met 45	tca Ser 30 ccc Pro	Asp 15 ggg Gly cca Pro	Trp tca Ser cgc Arg	96 144

Ile 65	Val	Ser	Trp	Phe	A1a 70	Asp	His	Pro	Arg	Ala 75	Pro	Phe	Gly	Leu	His 80		
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												gcc Ala					336
												cag Gln 125					384
												cca Pro					432
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									-		-	gaa Glu		_	_		528
												cga Arg					576
		Ile	Gly	Tyr	Gln		Asp	Phe	Leu	Leu	Tyr	ctg Leu 205	Asp			ı	624
Tyr								-	_	Ala	-	ttc Phe		_		(672
			-	Thr	-		-	_	Met	-		gcc Ala	-	_	-		720
cca	agc	tgt	acc	gtg	ggc	ttc	tat	gct	gga	gac	agg	aag	gag	ttt	gag	-	768

Pro	Ser	· Cys	Thr	Val 245	Gly	Phe	Tyr	Ala	Gly 250	-	Arg	Lys	Glu	Phe 255		
						acc Thr										816
			Pro			acc Thr										864
		Asp				tcc Ser- 295			-	_						912
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			tta Leu	taa *												975
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Thr	Trp	Ala	G1u 20		Met	Gly		G1 y 25		Pro	Glu	Leu	Ser 30		Ser	
Ala	Ser	Pro 35		Arg	Tyr	His			Ala	Arg	Trp	Met 45		Pro	Arg	
Trp	A1a 50	Gln	Gly	Ala		G1u 55	Leu	Glu	Gln	Glu	Arg 60	Arg	His	Arg	G1n	
He	Val	Ser	Trp	Phe	Ala	Asp	His	Pro	Arg	Ala	Pro	Phe	Gly	Leu	His	

223

65 70 75 Arg Leu Val Glu Leu Gly Gln Ser Ser Gly Lys Lys Ala Gly Asp Trp Tyr Gly Pro Ser Leu Val Ala His Ile Leu Arg Lys Ala Val Glu Ser 100 105 Cys Ser Asp Val Thr Arg Leu Val Val Tyr Val Ser Gln Asp Cys Thr 120 Val Tyr Lys Ala Asp Val Ala Arg Leu Val Ala Arg Pro Asp Pro Thr 135 140 Ala Glu Trp Lys Ser Val Val Ile Leu Val Pro Val Arg Leu Gly Gly 150 Glu Thr Leu Asn Pro Val Tyr Val Pro Cys Val Lys Glu Leu Leu Arg 170 Cys Glu Leu Cys Leu Gly Ile Met Gly Gly Lys Pro Arg His Ser Leu 185 Tyr Phe Ile Gly Tyr Gln Asp Asp Phe Leu Leu Tyr Leu Asp Pro His 200 Tyr Cys Gln Pro Thr Val Asp Val Ser Gln Ala Asp Phe Pro Leu Glu 215 Ser Phe His Cys Thr Ser Pro Arg Lys Met Ala Phe Ala Lys Met Asp 230 235 Pro Ser Cys Thr Val Gly Phe Tyr Ala Gly Asp Arg Lys Glu Phe Glu 250 Thr Leu Cys Ser Glu Leu Thr Arg Val Leu Ser Ser Ser Ser Ala Thr 265 Glu Arg Tyr Pro Met Phe Thr Leu Ala Glu Gly His Ala Gln Asp His 280 Ser Leu Asp Asp Leu Cys Ser Gln Leu Ala Gln Pro Thr Leu Arg Leu 295 300 Pro Arg Thr Gly Arg Leu Leu Arg Ala Lys Arg Pro Ser Ser Glu Asp 310 315 Phe Val Phe Leu

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<220>

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_				_	tct Ser	_	_				-		-	-		192
-	-	-		-	aag Lys 70			-				_				240
				_	tgt Cys		-		_		_			_	_	288
-					tac Tyr										-	336
					tgg Trp		-					_	_			384
	_				gcg Ala		_					_				432
-					acg Thr 150					-						480
					aag Lys											528

			Tyr	Arg				Tyr	Phe				Val	caa G1n		57	6
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			Arg											gtc Val		62	4
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	<; <;	211> 212> 213>			pien	S											
Mot			158 Val	GIV	يرم ا	Trn	يرم ا	בוז	Gln	Trn	Lou	Lou	Lou	Lys	Tun		
1	116	LCU	Vai	5	LEU	пр	Leu	116	10	пр	Ļeu	Leu	Leu	Lys 15	Tyr		
Lÿs	Ser	Ile	Ile 20	Ser	Arg	Arg	Phe	Phe 25	Cys	Ile	Val	Gly	Thr 30	Leu	Tyr		
Leu	Tyr	Arg 35	Cys	He	Thr	Met	Tyr 40	۷al	Thr	Thr	Leu	Pro 45	Val	Pro	Gly		
Met	His 50	Phe	Asn	Cys	Ser	Pro 55	Lys	Leu	Phe	Gly	Asp 60	Trp	Glu	Ala	Gln		
Leu 65	Arg	Arg	Ile	Met	Lys 70	Leu	Ile	Ala	Gly	Gly 75	Gly	Leu	Ser	Ile	Thr 80		
Gly	Ser	His	Asn	Met 85	Cys	Gly	Asp	Tyr	Leu 90	Tyr	Ser	Gly	His	Thr 95	Val		
1 et	Leu	Thr	Leu 100	Thr	Tyr	Leu	Phe	Ile 105	Lys	Glu	Tyr	Ser	Pro 110	Arg	Arg		
_eu	Trp	Trp 115	Tyr	His	Trp	Ile	Cys 120	Trp	Leu	Leu	Ser	Val 125	Val	Gly	Ile		
Phe	Cys 130	He	Leu	Leu	Ala	His 135	Asp	His	Tyr	Thr	Val 140	Asp	Val	Val	Val		
	Tyr	Tyr	Пe	Thr		Arg	Leu	Phe	Trp		Tyr	His	Thr	Met			
l45 \sn	Gln	Gln	Val	Leu 165	150 Lys	Glu	Ala	Ser	G1n 170	155 Met	Asn	Leu	Leu	Ala	160 Arg		
/al	Trp	Trp	Tyr 180		Pro	Phe	Gln	Tyr 185		Glu	Lys	Asn	Val 190	175 G1n	Gly		
۵۱	Val	Dro		San	Tyr	∐ic.	Trn		Dha	Dno	Tnn	Dno		Val	مناا		

Leu				Val	Lys	-		Leu	Val	Asn	205 Asp			
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								ccg Pro						• 96
								ctg Leu						144
								cgg Arg						192
								gga Gly						240
					His			gac Asp 90						288
								cat His						336

			100					105					110				
												cct Pro 125			•		384
							-				_	agc Ser	-		•		432
												ccg Pro					480
												aat Asn					528
	cga Arg															!	540
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Leu	Leu	Leu	Ala 20	Ser	Gln	Val	Leu	Ser 25	Pro	Gly	Ser	Cys	A1a 30		Glu		
		35				·	40					Va1 45					
	50					55			-		60	His					
He 55	Val	Leu	Arg		Arg 70	Thr	Xaa	Lys	Gly	Asp 75	Ala	Asp	Leu	Tyr	Val 80		

Ser	Ala	Ser	Ser	Leu 85	His	Pro	Ser	Phe	Asp 90	Asp	Tyr	Glu	Leu	G1n 95	Ser	
Ala	Thr	Xaa	Arg 100		Gly	Arg	Arg	Val 105		Pro	Arg	Ala	Leu 110		Ala	
Pro	Ser	Gly 115		Arg	Arg	Leu	Trp 120	Thr	Pro	Leu	Pro	Pro 125	Gly	Glu	Arg	
Val	Arg 130			Gly	Val	Leu 135	Arg	Arg	His	Gly	Xaa 140		Ser	Thr	Arg	
Ser 145		Arg	Pro	Pro	Thr 150		Pro	Thr	Ala	Gln 155		Pro	Ala	Arg	Ser 160	
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		-		-		-	ggg Gly					-	-			96
			gcg				atg Met 40									144
Gly gag	Pro aag	Gly 35 ctg	gcg Ala aag	Ala ctg	Tyr ctc	His cgc	Met	Phe gag	Val gag	Val gag	Met ttc	G1u 45 ctc	Asp cgg	Leu aag	Va]l agc	144

	-	_			_	ttt Phe	-			-	_		_			288
			-			gag Glu	_			_		-	_			336
•						cta Leu								-		384
_	-					aaa Lys 135		_					-		-	432
-		-		-	_	ttc Phe	-	-	_	-	_					480
						ata Ile			-	-	-		-	-	-	528
-	-	-	-	_	-	gca Ala	-						-	-	-	576
-			-	-		aca Thr	-		-	-				-		624
	_		_	-	_	aca Thr 215			_	-	-				_	672
		-	_		_	gaa Glu				-	_					720
	_		-	-	-	cta Leu	-		-		-	_				768

-		_			_					_	cac His	-		_	816
											ttt Phe 285				864
			-								agc Ser	-	_	-	912
											gaa Glu				960
-		-	_	_	_		-	_	 _		cag Gln	•			1008
											gtt Val	_	_	•	1056
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Leu	His 290	Asn	Glu	Ile	Thr	Arg 295		Leu	G1u	Lys	Ile 300	Ser	Ser	Arg	Glu	
Lys 305	Tyr	Ile	Asn	Asn	Gln 310	Leu	Glu	Asn	Leu	Val 315	Gln	Glu	Tyr	Arg	A1a 320	
	Gln	Ala	Gln	Leu 325	Ser	Glu	Ala	Lys	G1u 330	Arg	Tyr	Gln	Gln	G1y 335		
Gly	Gly	Val	Thr 340		Arg	Thr	Arg	Leu 345		Ser	Glu	Val	Met 350		Glu	
Leu	Glu	Lys 355		Lys	Gln	Glu	Met 360		Glu	Lys	Gly	Ser 365	Ser	Met	Thr	
Asp	G1y 370	Ala	Pro	Leu	۷a۱	Lys 375	Ile	Lys	Gln	Ser	Leu 380	Thr	Lys	Leu	Lys	
G1n 385	Glu	Thr	Val	Glu	Met 390	Asp	Ile	Arg	He	G1y 395	Ile	Val	Glu	His	Thr 400	
Leu	Leu	Gln	Ser	Lys 405	Leu	Lys	Glu	Lys	Ser 410	Asn	Met	Thr	Arg	Asn 415	Met	
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													gag Glu			144
									_				aac Asn			192

			aag Lys										_	-	_	240
			gcc Ala		-	-										288
	-		ttg Leu 100												-	336
-	_		aag Lys													384
	_	-	tta Leu		_				-		_	-			-	432
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Ala	Tyr	Ile 35	Arg	Arg	Cys	Ala	Cys 40		Ala	Ser	Ser	Asp 45		Ser	Pro	
Gly	Ser 50		Cys	Ser	Pro	G1u 55	Asp	Leu	Ala	Thr	A1a 60	Tyr	Asn	Asn	Arg	
Gly 65		Пe	Lys	Tyr	Phe 70		Val	Asp	Phe	Tyr 75		Ala	Met	Asp	Asp 80	
Tyr	Thr	Ser	Ala	I1e 85	Glu	Val	Gln	Pro	Asn 90	Phe	Glu	Val	Pro	Tyr 95	Tyr	

			100					105					110	Ala		
Glu	Asp	Phe 115	Lys	Lys	Val	Leu	Asp 120	Leu	Asn	Pro	Gly	Phe 125	Gln	Asp	Ala	
Thr	Leu 130		Leu	Lys	Gln	Thr 135		Leu	Asp	Lys	Glu 140		Lys	Gln	Arg	
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														tct Ser		144
	_						_	_			_		_	atg Met	-	192
														aag Lys		240
_														gga Gly 95		288
ttt	caa	gga	agt	caa	aaa	gat	aat	tgg	gga	cat	ttt	aga	ctt	aag	aag	336

	Phe	G1n	Gly	Ser 100		Lys	Asp	Asn	Trp 105		His	Phe	Arg	Leu 110	-	Lys	
				Asp										Ser		cct Pro	384
			Gly	cag Gln									Ala			tca Ser	432
		Trp		tgt Cys								Leu					480
				act Thr													528
				gaa Glu 180													576
				ccc Pro								Lys					624
				ttt Phe										-	•		672
				cat His													720
				tgg Trp					Ser								768
				ttg Leu 260				Gly									816
,	gag	ctc	999	gtc	ctt	ttc	ctc	cct	tca	gca	ttt	ggt	cta	gac	agt	ttc	864

Glu	Leu	Gly 275	Val	Leu	Phe	Leu	Pro 280	Ser	Ala	Phe	Gly	Leu 285	Asp	Ser	Phe	
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		-	cca Pro		_	_			-	-			_		•	960
			ata Ile						-			-	-	_		1008
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		100>) Sah	on ens	•										
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1 Ser	Met Asn	100> Leu Leu Pro	166 Leu	Leu 5 His	Tyr Ala	Glu Asp	Trp Ile	His 25	10 Gln	Lys	Thr	Gln His	Gly 30	15 Ile	Trp	
1 Ser Leu	Met Asn Ser	100> Leu Leu Pro 35	166 Leu Ile 20	Leu 5 His Tyr	Tyr Ala Pro	Glu Asp Arg Lys	Trp Ile 40	His 25 Ala	10 Gln Asp	Lys Gly	Thr Thr Ser	Gln His 45	Gly 30 Lys	15 Ile Ser	Trp Gly	
1 Ser Leu Glu Tyr	Met Asn Ser Ser 50	Leu Pro 35 Pro	166 Leu Ile 20 Leu	Leu 5 His Tyr	Tyr Ala Pro	Glu Asp Arg Lys 55	Trp Ile 40 Ala	His 25 Ala Asp	10 Gln Asp Leu	Lys Gly Ile Asp	Thr Thr Ser 60	Gln His 45 Tyr	Gly 30 Lys Leu	15 Ile Ser Met	Trp Gly Ala His	
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l Ser Leu Glu Tyr 65 Asp	Met Asn Ser Ser 50 Asn Leu	Leu Pro 35 Pro Ala	166 Leu Ile 20 Leu Thr Pro Glu Ser	Leu 5 His Tyr His Ser Thr 85	Tyr Ala Pro Phe Leu 70 Asn	Glu Asp Arg Lys 55 Lys Val	Trp Ile 40 Ala Glu Tyr	His 25 Ala Asp Trp Leu Trp	10 Gln Asp Leu Ile Ile 90	Lys Gly Ile Asp 75 Gly	Thr Thr Ser 60 Val	Gln His 45 Tyr Ile Thr	Gly 30 Lys Leu His Pro	15 Ile Ser Met Lys Gly 95	Trp Gly Ala His 80 Arg	
1 Ser Leu Glu Tyr 65 Asp	Met Asn Ser Ser 50 Asn Leu Gln	HOO> Leu Pro 35 Pro Ala Ser Gly	166 Leu Ile 20 Leu Thr Pro Glu	Leu 5 His Tyr His Ser Thr 85 Gln	Tyr Ala Pro Phe Leu 70 Asn	Glu Asp Arg Lys 55 Lys Val Asp	Trp Ile 40 Ala Glu Tyr Asn	His 25 Ala Asp Trp Leu Trp 105	10 Gln Asp Leu Ile Ile 90 Gly	Lys Gly Ile Asp 75 Gly His	Thr Thr Ser 60 Val Ser Phe	Gln His 45 Tyr Ile Thr	Gly 30 Lys Leu His Pro Leu 110	15 Ile Ser Met Lys Gly 95 Lys	Trp Gly Ala His 80 Arg Lys	

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	Ser	Lys	Thr	Pro 165		Lys	Ser	Ser	Val 170		Leu	Tyr	Leu	Ile 175			
Pro	Ser	Val	Glu 180		Val	Arg	Thr	Ser 185		Glu	Gly	Tyr	Pro 190	Ala	Gly		
Gly	.Ser	Leu 195		Tyr	Ser	Ile	G1n 200		Ala	Glu	Lys	Gln 205		Trp	Leu		
His	Ser 210		Phe	His	Lys	Trp 215		Ala	Glu	Thr	Ser 220		Arg	Ser	Asn		
A1a 225		Pro	His	Пe	Lys 230		Tyr	Met	Arg	Pro 235		Pro	Asp	Phe	Ser 240		
	Ile	Ala	Trp	Phe 245		Val	Thr	Ser	A1a 250		Leu	Ser	Lys	A1 a 255			
Trp	Gly	Ala	Leu 260		Lys	Asn	Gly	Thr 265		Leu	Met	Ile	Arg 270	Ser	Tyr		
Glu	Leu	Gly 275		Leu	Phe	Leu	Pro 280		Ala	Phe	Gly	Leu 285		Ser	Phe	•	
Lys	Va1 290	Lys	Gln	Lys	Phe	Phe 295	Ala	Gly	Ser	G1n	G1u 300	Pro	Met	Ala	Thr		
Phe 305	Pro	Val	Pro	Tyr	Asp 310	Leu	Pro	Pro	G1u	Leu 315	Tyr	Gly	Ser	Lys	Asp 320		
Arg	Pro	Trp	Ile	Trp 325	Asn	Пe	Pro	Tyr	Va1 330	Lys	Ala	Pro	Asp	Thr 335	His		
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				tgc Cys	_			-					_		192
-	-		_	ctt Leu											240
				acc Thr 85											288
_	_		_	gcc Ala											336
	-		_	cgg Arg	_	_	_								384
			_	aca Thr					-						432
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Phe Phe Thr Phe Cys Cys Gly Thr Cys Tyr His Arg Tyr Cys Cys Arg
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Asp Leu Thr Leu Leu Ile Thr Glu Arg Gln Gln Lys His Cys Leu Ala
Phe Ser Pro Lys Thr Ile Ala Gly Ile Ala Ser Ala Val Ile Leu Phe
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Val Ala Val Val Ala Thr Thr Ile Cys Cys Phe Leu Cys Ser Cys Cys
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Tyr Leu Tyr Arg Arg Arg Gln Gln Leu Gln Ser Pro Phe Glu Gly Gln
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Glu Ile Pro Met Thr Gly Ile Pro Val Gln Pro Val Tyr Pro Tyr Pro
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Gln Asp Pro Lys Ala Gly Pro Ala Pro Pro Gln Pro Gly Phe Met Tyr
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Pro Pro Ser Gly Pro Ala Pro Gln Tyr Pro Leu Tyr Pro Ala Gly Pro
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Ser 65	Arg	Asn	Leu	Leu	Arg 70	Pro	Pro	Leu	His	Trp 75	Val	Leu	Leu	Ala	Leu 80	
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Leu	Ala	Val	Ser 100	Leu	Thr	Val	Ala	Asn 105	Gly	Gly	Arg	Arg	Leu 110	IJе	Ala	
Asp	Cys	His 115	Pro	Gly	Leu	Leu	Asp 120	Pro	Leu	Val	Pro	Leu 125	Asp	Glu	Gly	
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Ala	Leu	Ser	Gly	Tyr 165	Cys	Cys	Val	Ala	Ala 170		Thr	Leu	Arg	Gly 175	Val	
Gly	Pro	Cys	Arg 180	Lys	Asp	Gly	Leu	Gln 185		Gln	Leu		Glu 190		Thr	

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PCT/US00/29052

243

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Tyr Lys *
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WO 01/29221

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Ala Leu His Leu Leu Ala Leu Leu Phe Ser Ala Gln Lys His His Gln
20 25 30

		_	-	-	-			gcc Ala								144
								aag Lys								192
		-	-				-	aga Arg			_	~ ~	•	~ ~	_	240
	_		_			_	_	gga Gly			_	_	-		•	288
								aag Lys 105	_	-		_		_		336
-		_	_		_	_	-	tct Ser					-	_		384
					_		-	gcc Ala	-			-		-		432
	_	-	_	Lys	_			atg Met	_	_			_	-	-	480
								ctg Leu								528
-	-		-		-		_	gag Glu 185								576
								ggc Gly								. 624

					-	cag Gln 215					-		_			672
						atg Met										720
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			20			Asn		25				-	30			
		35					40					45				
rne	Asn 50	Leu	met	rne	ınr	Lys 55	val	Lys	Leu	ыu	GIN 60	val	Leu	Lys	ыу	

Pro Glu Glu Ala Leu Val Thr Cys Arg Gln Val Leu Arg Leu Trp Gln 70 Thr Leu Tyr Ser Phe Ser Gln Leu Gly Gly Leu Glu Lys Asp Gly Ser 90 85 Phe Gly Glu Gly Leu Thr Met Lys Lys Gln Ser Gly Met His Leu Thr 105 Leu Pro Asp Ala His Asp Ala Asp Ser Gly Ser Arg Arg Ala Ser Ser 120 Ile Ala Ala Ser Arg Leu Glu Glu Ala Met Ser Glu Leu Thr Met Pro 130 135 Ser Ser Val Leu Lys Gln Gly Pro Met Gln Leu Trp Thr Thr Leu Glu 150 155 Gln Ile Trp Leu Gln Ala Ala Glu Leu Phe Met Glu Gln Gln His Leu 165 170 Lys Glu Ala Gly Phe Cys Ile Gln Glu Ala Ala Gly Leu Phe Pro Thr 180 185 Ser His Ser Val Leu Tyr Met Arg Gly Arg Leu Ala Glu Val Lys Gly 195 200 205 Asn Leu Glu Glu Ala Lys Gln Leu Tyr Lys Glu Ala Leu Thr Val Asn 215 220 Pro Asp Gly Val Arg Ile Met His Ser Leu Gly Leu Met Leu Ser Arg 230 235 Leu Gly His Lys Ser Leu Ala Gln Lys Val Leu Arg Asp Ala Val Glu 245 250 Arg Gln Ser Thr Cys His Glu Ala Trp Gln Gly Leu Gly Glu Val Leu 265 270 Gln Ala Gln Gly Gln Asn Glu Ala Ala Val Asp Cys Phe Leu Thr Ala 280 285 Leu Glu Leu Glu Ala Ser Ser Pro Val Leu Pro Phe Ser Ile Ile Pro 290 295 300 Arg Glu Leu 305 <210> 175 <211> 627 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(627) <221> misc feature <222> (1)...(627)

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taa *																627
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Gly	Ser	Lys	Phe	Asp 165	Thr	Gly	Ser	Phe	Val 170	Gly	Gly	Ile	Val	Leu 175	Thr	
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ggg aa Gly Ly	_	-				-	-		_	-	_	-			336
ttc to Phe Se					-		_	_			_	_			384
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caa ga Gln Gl 145															480
gct ga Ala As	-	-	-	-		-		_				-	-		528
gca gc Ala Al		-									_				576
acg gg Thr Gl	-	_					-	-	-			-			624
gac ta Asp Ty 21	r Asp	_	-			-	-			-					672
atc ct Ile Le 225	_				_	_			-				-	_	720
ttc ca Phe Hi	_	_	_			-	•				-	_	-		768

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					cgc Arg												912
					cga Arg 310				-			-	_		-		960
					gag Glu											-	1008
					gcc Ala					-		_	_	_		1	1056
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					ccc Pro 390											1	200
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252

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253

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·	370			Glu	•	375					380				
385	-	,		Ile	390					395				·	400
	·	·	•	Leu 405					410	•				415	•
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-			_		_	_			-		gat Asp 220		_	_	~	672
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257

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258

gca atg gct ttc cag gtc cca ccc aac tca ccc cag ggg agt gtg gcc 336 Ala Met Ala Phe Gln Val Pro Pro Asn Ser Pro Gln Gly Ser Val Ala 100 105 110 tgc ccg ccc cct cca gcc tac tgc aac acg cct ccg ccc ccg tac qaa 384 Cys Pro Pro Pro Pro Ala Tyr Cys Asn Thr Pro Pro Pro Pro Tyr Glu 115 120 cag gta gtg aag gcc aag tag 405 -Gln Val Val Lys Ala Lys * 130 <210> 182 <211> 134 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(134) <223> Xaa = Any Amino Acid <400> 182 Met Pro Leu Leu Arg Gly Leu Leu Trp Leu Gln Val Leu Cys Ala Gly 10 Pro Leu His Thr Glu Ala Val Val Leu Leu Val Pro Ser Asp Asp Gly Arg Ala Phe Leu Leu Arg Xaa Gly Phe Phe Ile Arg Arg Arg Met Tyr 40 Pro Pro Pro Leu Ile Glu Glu Pro Ala Phe Asn Val Ser Tyr Thr Arg Gln Pro Pro Asn Pro Gly Pro Gly Ala Gln Gln Pro Gly Pro Pro Tyr 70 75 Tyr Thr Asp Pro Gly Gly Pro Gly Met Asn Pro Val Gly Asn Ser Met Ala Met Ala Phe Gln Val Pro Pro Asn Ser Pro Gln Gly Ser Val Ala 105 110 Cys Pro Pro Pro Pro Ala Tyr Cys Asn Thr Pro Pro Pro Pro Tyr Glu 115 120 125 Gln Val Val Lys Ala Lys 130

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WO 01/29221

PCT/US00/29052

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												agc Ser 30			96
_	-			_	_		 		-		_	ttc Phe	_		144
												gac Asp			192
				-				_	_	-		gag Glu			240
												ttt Phe			288
												tgc Cys 110			336
												tgc Cys			384

									ctg Leu			432
									aga Arg			480
									agg Arg			528
									tca Ser 190		_	576
									cac His			624
									ctc Leu			672
		-	 		-			-	atc Ile	_	-	720
	_		-				-	-	ctc Leu		_	768
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Gly				aag Lys 295				tga *				900

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				245	,				250					255	1	
Glu	Asp	Val	Va1 260	Leu		Ile	Tyr	Cys 265	Gly		Val	Gly	Phe 270	Leu		
Val	Leu	Thr 275		Thr	His	Phe	G1 <i>y</i> 280		Leu	Ala	Ser	Pro 285	Phe		Ser	
Gly	Leu 290		Leu	Leu	Gly	Lys 295		Lys	Thr	Arg						
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													Gln			48
							-	-	-		_	_	att Ile 30			96
													aaa Lys			144
													cta Leu			192
													atg Met			240
													ttt Phe			288
													ctt Leu			336

263

100 105 110 cga ctt tgt tac ctg aaa gag cag gaa gat att gca tgg tct gct ctt 384 Arg Leu Cys Tyr Leu Lys Glu Gln Glu Asp Ile Ala Trp Ser Ala Leu 115 120 125 gtg aag ttg ttt gat ccc gtg aaa tct ccc aga tgt tat gct gtt att 432 Val Lys Leu Phe Asp Pro Val Lys Ser Pro Arg Cys Tyr Ala Val Ile 130 135 140 gcc ctg aag aag cag cag tga 453 Ala Leu Lys Lys Gln Gln * 145 150 <210> 186 <211> 150 <212> PRT <213> Homo sapiens <400> 186 Met Ser Ala Cys Leu Ala Leu Glu Arg Val Ala Ala Gly Gln Gly Leu 10 Pro Thr Glu Ser Leu Phe Tyr Arg Ala Val Leu Gln Asp Ile Ile Lys 25 Asp Cys Tyr Gly Ile Thr Lys Cys Asp Arg His Val Gly Lys Ile Tyr 40 45 Ser Lys Cys Ser Ser Phe Leu Asp Tyr Val Arg Arg Ser Leu Lys Lys 55 60 Leu Gly Leu Asp Glu Ser Lys Leu Pro Glu Lys Ile Ile Met Asn Tyr 70 75 Tyr Glu Lys Tyr Lys Pro Arg Met Asn Glu Leu Glu Ala Phe Asn Met 90 Leu Lys Val Val Leu Ala Pro Cys Ile Glu Thr Leu Ile Leu Leu Asp 105 100 110 Arg Leu Cys Tyr Leu Lys Glu Gln Glu Asp Ile Ala Trp Ser Ala Leu 120 125 Val Lys Leu Phe Asp Pro Val Lys Ser Pro Arg Cys Tyr Ala Val Ile 135 140 Ala Leu Lys Lys Gln Gln 145 150 <210> 187 <211> 1491

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-				_	_		-	_					ccc Pro	_		144
													gcg Ala			192
				-					-		-		gtc Val			240
-	_	-	_							-	_	_	gca Ala 95			288
		_						-		_	-		tca Ser			336
	_	_	-	-	-					_	-		gca Ala	_	;	384
					-		_	-			-		gcc Ala			432

											gta Val					480
-				_			-	_			gat Asp		_	-		528
	_										ctt Leu			_		576
											gat Asp					624
					-		-				cag Gln 220			-		672
,	_		-						-		tcc Ser			-	_	720
											gag Glu					768
		-						_	_		gga Gly		-	-		816
	_		-	-		Leu	-	-	-		tcc Ser			_		864
					-				-	-	agt Ser 300	_				912
-								-	-		ccc Pro					960

	999 Gly	-			-		-					_		_		1008
	cct Pro										_		•	~ ~		1056
_	gtc Val	_	-						-		•			~~	_	1104
	agc Ser 370															1152
	cac His		_	_									_	_	_	1200
•	gtg Val	-	_		-	-		-			-	-	-	-		1248
_	acc Thr		-		-	-			_		_					1296
_	act Thr			_		-					-					1344
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	gta Val								_							1440
-	att Ile			-					_	_	_					1488

267

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Leu Val Val Leu Ser Gly Leu His Met Met Glu Gly Gln Ser Lys Glu

			260					265					270			
Leu	Gln	Arg 275	Lys	Arg	Leu	Leu	G1u 280			Thr	Ser	Ile 285		Asp	Ile	
Pro	Thr 290	Gly	Ile	Pro	Val	His 295	Leu	Glu	Leu	Ala	Ser 300	Met	Thr	Asn	Arg	
G1u 305	Leu	Met	Ser	Ser	Ile 310	Val	His	Gln	Val	Phe 315	Pro	Ala	Val	Thr	Ser 320	
Leu	Gly	Leu	Asn	G1u 325	Gln	Glu	Leu	Leu	Phe 330	Leu	Thr	Gln	Ser	A1a 335	Ser	
Gly	Pro	His	Ser 340	Ser	Leu	Ser	Ser	Trp 345	Asn	Gly	Val	Pro	Asp 350	Val	Gly	
Met	Val	Ser 355	Asp	Ile	Leu	Phe	Trp 360	Пe	Leu	Lys	Glu	His 365	Gly	Arg	Ser	
Lys	Ser 370	Arg	Ala	Ser	Asp	Leu 375	Thr	Arg	Ile	His	Phe 380	His	Thr	Leu	Val	
Tyr 385	His	Пe	Leu	Ala	Thr 390	Val	Asp	Gly	His	Trp 395	Ala	Asn	Gln	Leu	A1a 400	
Ala	Val	Ala	Ala	Gly 405	Ala	Arg	Val	Ala	Gly 410	Thr	Gln	Ala	Cys	Ala 415	Thr	
Glu	Thr	Ile	Asp 420	Thr	Ser	Arg	Val	Ser 425	Leu	Arg	Ala	Pro	G1n 430	Glu	Phe	
Met	Thr	Ser 435	His	Ser	Glu	Ala	G1y 440	Ser	Arg	Пe	Val	Leu 445	Asn	Pro	Asn	
Lys	Pro 450	Val	Val	Glu	Trp	His 455	Arg	Glu	Gly	Ile	Ser 460	Phe	His	Phe	Thr	
Pro 465	Val	Leu	Val	Cys	Lys 470	Asp	Pro	Ile	Arg	Thr 475	Val	Gly	Leu	Gly	Asp 480	
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			-		gcc Ala							96
	 -			-	gaa Glu 40	_	_	_	_		_	 144
					ttg Leu							192
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tga *												339

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 Pro Gly Thr Ala Ala Ala Pro Ala Lys Pro Ala Pro Pro Ala Thr Pro 20
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 Gly Ala Pro Thr Ser Pro Ala Glu His Arg Leu Leu Lys Thr Cys Trp 35
 40
 45

 Ser Cys Arg Val Leu Ser Gly Leu Gly Leu Met Gly Ala Gly Gly Tyr 50
 55
 60

 Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser

65 Pro	Trp	Thr	Ile	Thr 85	70 G1n	Met	Val	Ile	G1y 90	75 Leu	Ser	Ile	Ala	Thr 95	80 Trp	
Gly	Пe	Val	Val 100		Ala	Asp	Pro	Lys 105		Lys	Ala	Tyr	Arg 110		Val	
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	gcg		gcc		gca Ala											48
_				_	agc Ser		_		_	_		_				96
-	-				tct Ser	-		-					_	_		144
					tat Tyr	-					-	_				192
					ctg Leu 70											240
					aag Lys											288
					gtg Val				-							336

acc Thr	tct Ser	gaa Glu 115	gac Asp	ctg Leu	atc Ile	tta Leu	att Ile 120	gga Gly	aat Asn	gaa Glu	cta Leu	gac Asp 125	ctt Leu	gcg Ala	tgt Cys		384
gga Gly	gag Glu 130	aga Arg	att Ile	cga Arg	ctg Leu	gag Glu 135	aag Lys	gtc Val	ctg Leu	ctg Leu	gtt Val 140	ggg Gly	gca Ala	gac Asp	aac Asn		432
						cca Pro											480
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	Gln					ata Ile										(624
ttg _eu	tga *															(530

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<213> Homo sapiens

<400> 192

Met Ala Ala Ala Met Ala Ala Ser Ser Leu Thr Val Thr Leu Gly Arg

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Leu Ala Ser Ala Cys Ser His Ser Ile Leu Arg Pro Ser Gly Pro Gly
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Ala Ala Ser Leu Trp Ser Ala Ser Arg Arg Phe Asn Ser Gln Ser Thr
35 40 45

Ser Tyr Leu Pro Gly Tyr Val Pro Lys Thr Ser Leu Ser Ser Pro Pro
50 55 60

Trp Pro Glu Val Val Leu Pro Asp Pro Val Glu Glu Thr Arg His His

65					70					75					80		
Ala	Glu	Val	Val	Lys 85	Lys	Val	Asn	Glu	Met 90	Пe	Val	Thr	Gly	G1n 95	Tyr		
Gly	Arg	Leu	Phe 100	Ala	Val	Val	His	Phe 105	Ala	Ser	Arg	Gln	Trp 110	Lys	Val		
Thr	Ser	Glu 115	Asp	Leu	Ile	Leu	Ile 120	Gly	Asn	Glu	Leu	Asp 125	Leu	Ala	Cys		
Gly	Glu 130	Arg	Ile	Arg	Leu	Glu 135	Lys	Val	Leu	Leu	Val 140	Gly	Ala	Asp	Asn	•	
Phe 145	Thr	Leu	Leu	Gly	Lys 150	Pro	Leu	Leu	Gly	Lys 155	Asp	Leu	Val	Arg	Val 160		
Glu	Ala	Thr	Val	Ile 165	Glu	Lys	Thr	Glu	Ser 170	Trp	Pro	Arg	Пe	Ile 175	Met		
Arg	Phe	Arg	Lys 180	Arg	Lys	Asn	Phe	Lys 185	Lys	Lys	Arg	Ile	Val 190	Thr	Thr		
Pro	G1n	Thr 195	Val	Leu	Arg	Ile	Asn 200	Ser	Ile	Glu	He	A1a 205	Pro	Cys	Leu		
Leu																	
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met 1	Gly	ser	Arg	5	ser	GIN	Pro	rne	10	5er	ıyr	1 ie	ınr	15	Pro		
	ggt															96	
Pro	Gly	Ihr	20	Ala	Ala	Pro	Ala	Lys 25	Pro	Ala	Pro	Pro	30	Ihr	Pro		
	gcg	_				-	-		_	_	_	_		_		144	
Gly	Ala	Pro 35	Thr	Ser	Pro	Ala	G1u 40	His	Arg	Leu	Leu	Lys 45	Thr	Cys	ſrp		
	tgt															192	
Ser	Cvc	Δra	Val	Leu	Sar	Glv	1011	GIV	انم ا	Met	GIV	Δla	Glv	GIV	Tvr		

273

50 55 60 gtg tac tgg gtg gca cgg aag ccc atg aag atg gga tac ccc ccg agt 240 Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser 75 65 70 80 cca tgg acc att acg cag atg gtc atc ggc ctc agt gag aat caa ggc 288 Pro Trp Thr Ile Thr Gln Met Val Ile Gly Leu Ser Glu Asn Gln Gly 90 85 att gcc acc tgg ggt atc gtt gtc atg gca gac ccc aaa ggg aag gcc 336 Ile Ala Thr Trp Gly Ile Val Val Met Ala Asp Pro Lys Gly Lys Ala 100 105 110 351 tac cgc gtt gtt tga Tyr Arg Val Val * 115 <210> 194 <211> 116 <212> PRT <213> Homo sapiens <400> 194 Met Gly Ser Arg Leu Ser Gln Pro Phe Glu Ser Tyr Ile Thr Ala Pro 5 Pro Gly Thr Ala Ala Ala Pro Ala Lys Pro Ala Pro Pro Ala Thr Pro 25 Gly Ala Pro Thr Ser Pro Ala Glu His Arg Leu Leu Lys Thr Cys Trp Ser Cys Arg Val Leu Ser Gly Leu Gly Leu Met Gly Ala Gly Gly Tyr 55 Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser 70 75 Pro Trp Thr Ile Thr Gln Met Val Ile Gly Leu Ser Glu Asn Gln Gly 90 Ile Ala Thr Trp Gly Ile Val Val Met Ala Asp Pro Lys Gly Lys Ala 100 105 110 Tyr Arg Val Val 115 <210> 195 <211> 1047

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		_		-				_			_			ctg Leu		1	44
				-		-	_	-		_	-		-	gca Ala	-	19	92
														atg Met		24	40
-	_						_	-		-			-	tca Ser 95		21	88
	_		-		_		-					_		agg Arg	_	33	36
														cac His		38	84
					Glu									gaa Glu		43	32

			gac Asp				Glu					480
			gag Glu									528
			atg Met									576
			act Thr									624
			gcc Ala 215								·	672
			ttg Leu									720
			acc Thr									768
			gcc Ala									816
gaa G1u			att Ile		-			_	_	-		864
Lys			caa G1n 295			Пe						912
act Thr 305		Ser			Leu				Phe		,	960

tta att agt ttt att atg tat gct acc att cga act gag agt att cgq 1008 Leu Ile Ser Phe Ile Met Tyr Ala Thr Ile Arg Thr Glu Ser Ile Arg 325 330 335 tgg cta att cca gga caa gag cag gaa cat gtg gag tag 1047 Trp Leu Ile Pro Gly Gln Glu Gln Glu His Val Glu * 340 345 <210> 196 <211> 348 <212> PRT <213> Homo sapiens <400> 196 Met Arg Leu Leu Gly Trp Trp Gln Val Leu Leu Trp Val Leu Gly Leu Pro Val Arg Gly Val Glu Val Ala Glu Glu Ser Gly Arg Leu Trp Ser Glu Glu Gln Pro Ala His Pro Leu Gln Val Gly Ala Val Tyr Leu Gly Glu Glu Glu Leu Leu His Asp Pro Met Gly Gln Asp Arg Ala Ala Glu 55 Glu Ala Asn Ala Val Leu Gly Leu Asp Thr Gln Gly Asp His Met Val Met Leu Ser Val Ile Pro Gly Glu Ala Glu Asp Lys Val Ser Ser Glu Pro Ser Gly Val Thr Cys Gly Ala Gly Gly Ala Glu Asp Ser Arg Cys 105 Asn Val Arg Glu Ser Leu Phe Ser Leu Asp Gly Ala Gly Ala His Phe 120 Pro Asp Arg Glu Glu Glu Tyr Tyr Thr Glu Pro Glu Val Ala Glu Ser 135 140 Asp Ala Ala Pro Thr Glu Asp Ser Asn Asn Thr Glu Ser Leu Lys Ser 145 150 155 Pro Lys Val Asn Cys Glu Glu Arg Asn Ile Thr Gly Leu Glu Asn Phe 165 170 Thr Leu Lys Ile Leu Asn Met Ser Gln Asp Leu Met Asp Phe Leu Asn 185 Pro Asn Gly Ser Asp Cys Thr Leu Val Leu Phe Tyr Thr Pro Trp Cys 200 205 Arg Phe Ser Ala Ser Leu Ala Pro His Phe Asn Ser Leu Pro Arg Ala 215 220 Phe Pro Ala Leu His Phe Leu Ala Leu Asp Ala Ser Gln His Ser Ser

225					230					235					240	*
Leu	Ser	Thr	Arg	Phe 245	Gly	Thr	Val	Ala	Va1 250	Pro	Asn	He	Leu	Leu 255		•
Gln	Gly	Ala	Lys 260	Pro	Met	Ala	Arg	Phe 265	Asn	His	Thr	Asp ·	Arg 270			
Glu	Thr	Leu 275	Lys	Ile	Phe	Пe	Phe 280	Asn	Gln	Thr	Gly	Ile 285	Glu	Ala	Lys	
Lys	Asn 290	Val	Val	Val	Thr	G1n 295	Ala	Asp	Gln	Ile	G1y 300	Pro	Leu	Pro	Ser	
Thr 305	Leu	Ile	Lys	Ser	Val 310	Asp	Trp	Leu	Leu	Val 315	Phe	Ser	Leu	Phe	Phe 320	•
Leu	Ile	Ser	Phe	Ile 325	Met	Tyr	Ala	Thr	Ile 330	Arg	Thr	Glu	Ser	I1e 335	Arg	
Trp	Leu	Ile	Pro 340	Gly	Gln	Glu	Gln	G1u 345	His	Val	Glu					
			444 Dna	o sap	oiens	5								,		
	<2	220> 221> 222>		(4	144)											
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						gga Gly	-					_		Gly	-	96
						aaa Lys										144
						ggc Gly 55										192
						gtg Val										240

278

70 65 75 80 gtg ata att cac gta gga gca ctg agc ttg aag gag tca cag gaa ctg 288 Val Ile Ile His Val Gly Ala Leu Ser Leu Lys Glu Ser Gln Glu Leu 85 90 95 gcc caa cat gca gca gaa ata gga gct gat ggc atc gct gtc att gca 336 Ala Gln His Ala Ala Glu Ile Gly Ala Asp Gly Ile Ala Val Ile Ala 110 100 105 ccq ttc ttc ctc aag cca tgg acc aaa gat atc ctg att aat ttc cta 384 Pro Phe Phe Leu Lys Pro Trp Thr Lys Asp Ile Leu Ile Asn Phe Leu 125 115 432 aaq qaa qtg gct gct gcg ccc ctg ccc tgc cat ttt att act atc aca Lys Glu Val Ala Ala Ala Pro Leu Pro Cys His Phe Ile Thr Ile Thr 130 135 140 ttc ctg cct tga 444 Phe Leu Pro * 145 <210> 198 <211> 147 <212> PRT <213> Homo sapiens <400> 198 Met Ala Phe Pro Lys Lys Leu Gln Gly Leu Val Ala Ala Thr Ile Thr Pro Met Thr Glu Asn Gly Glu Ile Asn Phe Ser Val Ile Gly Gln 25 Tyr Val Asp Tyr Leu Val Lys Glu Gln Gly Val Lys Asn Ile Phe Val 40 Asn Gly Thr Thr Gly Glu Gly Leu Ser Leu Ser Val Ser Glu Arg Arg 55 60 Gln Val Ala Glu Glu Trp Val Thr Lys Gly Lys Asp Lys Leu Asp Gln Val Ile Ile His Val Gly Ala Leu Ser Leu Lys Glu Ser Gln Glu Leu 90 85 Ala Gln His Ala Ala Glu Ile Gly Ala Asp Gly Ile Ala Val Ile Ala 100 105 Pro Phe Phe Leu Lys Pro Trp Thr Lys Asp Ile Leu Ile Asn Phe Leu

	Glu 130 Leu			Ala	Ala	Pro 135	120 Leu	Pro	Cys	His	Phe 140	125 Ile	Thr	Ile	Thr	
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	_	_	-		gta Val	-	-	-								96
	_	-			ttc Phe		-	_	_	_		-			-	144
					gtg Val											192
		-		-	ctt Leu 70	-										240
					gga Gly											288

	999 Gly								_		_		_		336
	aat Asn														384
	atg Met 130														432
	aaa Lys														480
	tcg Ser	-	-	-				_						-	528
	ggt Gly			-	-	-				_	-	_	_		576
	act Thr				-	-		_				-			624
	tgt Cys 210		-			_			-		-	_	_		672
-	ctt Leu	_		-		_	-	_	tga *						705

<210> 200

<211> 234

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(234) <223> Xaa = Any Amino Acid

<400> 200 Met Met Ser Gln Gly Ser Gln Phe Leu Tyr Ser Thr Phe Gly Tyr Thr Leu Leu Ala Ala Ile Val Glu Arg Ala Ser Gly Cys Lys Tyr Leu Asp Tyr Met Gln Lys Ile Phe His Asp Leu Asp Met Leu Thr Thr Val Gln 40 Glu Glu Asn Glu Pro Val Ile Tyr Asn Arg Ala Arg Phe Tyr Val Tyr Asn Lys Lys Lys Arg Leu Val Asn Thr Pro Tyr Val Asp Asn Ser Tyr 70 75 Lys Trp Ala Gly Gly Gly Phe Leu Ser Thr Val Gly Asp Leu Leu Lys 90 Phe Gly Asn Ala Met Leu Tyr Gly Tyr Gln Val Gly Leu Phe Lys Asn 100 105 Ser Asn Glu Asn Leu Leu Pro Gly Tyr Leu Lys Pro Glu Thr Met Val 120 Met Met Trp Thr Pro Val Pro Asn Thr Glu Met Ser Trp Asp Lys Glu 135 140 Gly Lys Tyr Ala Met Ala Trp Gly Val Val Glu Xaa Lys Gln Thr Tyr 155 150 Gly Ser Cys Arg Lys Gln Arg His Tyr Ala Ser His Thr Gly Gly Ala 165 170 Val Gly Ala Ser Ser Val Leu Leu Val Leu Pro Glu Glu Leu Asp Thr 185 Glu Thr Ile Asn Asn Lys Val Pro Pro Arg Gly Ile Ile Val Ser Ile 200 Ile Cys Asn Met Gln Ser Val Gly Leu Asn Ser Thr Ala Leu Lys Ile 215

<210> 201

225

<211> 885

<212> DNA

<213> Homo sapiens

Ala Leu Glu Phe Asp Lys Asp Arg Ser Asp

230

<220>

<221> CDS

<222> (1)...(885)

	<	221> 222> 223>	(1)	(8	885)											
	ctg		gtg			ctg Leu										48
1	Leu	Ala	VQI	5	vai	Leu	Ala	Ala	10	Arg	Gly	diy	Ash	15	va i	
	_	-		_	-	aac Asn	-				-		-		_	96
				-		gac Asp				_		-		_		144
						ctg Leu 55										192
				-		gtg Val	-			-	_		_		_	240
	-		_			gag Glu	_			-	-	-				288
						agt Ser									_	336
						gag Glu										384
						ggt Gly 135			_						_	432
						gct Ala		_	_	_						480

283

gtg aaa gcc cgc tct tcc tac aat gag aag acc cca agg ntc gtt gtg Val Lys Ala Arg Ser Ser Tyr Asn Glu Lys Thr Pro Arg Xaa Val Val 165 170 175	528
tct cgt tcc cat tca ggg atg gtc aaa cag gtc gct ctt cag act ttt Ser Arg Ser His Ser Gly Met Val Lys Gln Val Ala Leu Gln Thr Phe 180 185 190	576
gga aac cag act aca att atc cca gct ggt ggt gct ggt tat aaa gtt Gly Asn Gln Thr Thr Ile Ile Pro Ala Gly Gly Ala Gly Tyr Lys Val 195 200 205	624
tta gca ctt ttg gat gtg cct gat aag agt caa gaa aaa gct gat tta Leu Ala Leu Leu Asp Val Pro Asp Lys Ser Gln Glu Lys Ala Asp Leu 210 215 220	672
tac atc cat gtg aca tac atc aaa aag tgg gat ata tgt gct ggt aat Tyr Ile His Val Thr Tyr Ile Lys Lys Trp Asp Ile Cys Ala Gly Asn 235 230 235 240	720
gcc atc tta aaa gcc cta ggg ggg cat atg act acc ctg agt ggt gaa Ala Ile Leu Lys Ala Leu Gly Gly His Met Thr Thr Leu Ser Gly Glu 245 250 255	768
gaa atc agt tac act ggt tca gac ggc att gaa ggg gga ctc ctt gct Glu Ile Ser Tyr Thr Gly Ser Asp Gly Ile Glu Gly Gly Leu Leu Ala 260 265 270	816
agc atc aga atg aac cac cag gcc ctg gtc aga aaa ctc cca gat cta Ser Ile Arg Met Asn His Gln Ala Leu Val Arg Lys Leu Pro Asp Leu 275 280 285	864
gaa aag aca gga cat aaa tga Glu Lys Thr Gly His Lys * 290	885
<210> 202 <211> 294 <212> PRT <213> Homo sapiens	

<220>

284

<221> VARIANT

<222> (1)...(294) <223> Xaa = Any Amino Acid <400> 202 Met Leu Ala Val Ser Val Leu Ala Ala Val Arg Gly Gly Asp Glu Val Arg Arg Val Arg Glu Ser Asn Val Leu His Glu Lys Ser Lys Gly Lys Thr Arg Glu Gly Ala Glu Asp Lys Met Thr Ser Gly Asp Val Leu Ser Asn Arg Lys Met Phe Tyr Leu Leu Lys Thr Ala Phe Pro Ser Val Gln 55 Ile Asn Thr Glu Glu His Val Asp Ala Ala Asp Gln Glu Val Ile Leu Trp Asp His Lys Ile Pro Glu Asp Ile Leu Lys Glu Val Thr Thr Pro 90 85 Lys Glu Val Pro Ala Glu Ser Val Thr Val Trp Ile Asp Pro Leu Asp 105 Ala Thr Gln Glu Tyr Thr Glu Asp Leu Arg Lys Tyr Val Thr Thr Met 120 Val Cys Val Ala Val Asn Gly Lys Pro Met Leu Gly Val Ile His Lys 135 Pro Phe Ser Glu Tyr Thr Ala Trp Ala Met Val Asp Gly Gly Ser Asn 150 · 155 Val Lys Ala Arg Ser Ser Tyr Asn Glu Lys Thr Pro Arg Xaa Val Val Ser Arg Ser His Ser Gly Met Val Lys Gln Val Ala Leu Gln Thr Phe 185 Gly Asn Gln Thr Thr Ile Ile Pro Ala Gly Gly Ala Gly Tyr Lys Val Leu Ala Leu Leu Asp Val Pro Asp Lys Ser Gln Glu Lys Ala Asp Leu 215 Tyr Ile His Val Thr Tyr Ile Lys Lys Trp Asp Ile Cys Ala Gly Asn 235 Ala Ile Leu Lys Ala Leu Gly Gly His Met Thr Thr Leu Ser Gly Glu 250 245 Glu Ile Ser Tyr Thr Gly Ser Asp Gly Ile Glu Gly Gly Leu Leu Ala 265 Ser Ile Arg Met Asn His Gln Ala Leu Val Arg Lys Leu Pro Asp Leu 275 280 285 Glu Lys Thr Gly His Lys 290

	<; <;				piens	S										
	<'	220> 221> 222>	CDS (1)	(8	361)											
	gag		aaa											gct Ala 15		48
														aag Lys		96
			_	_			_			_				cat His		144
		-	_						_		_	_	-	gta Val	_	192
_	_				_			-	_					gaa Glu		240
-										_	_			ggc Gly 95		288
														caa G1n		336
-				_					-		-			tat Tyr	_	384
		-			-				_					tat Tyr		432

286

	130			,		135					140					
-			-	_	cca Pro 150								_	~		480
	-		-		gaa Glu											528
	-				cgc Arg			-	-	-		-			-	576
-	_	_			cta Leu		-									624
		_		_	acá Thr			_	-	_	_				_	672
			_		aca Thr 230			-		-	-			_	-	720
			_		atc Ile	_	-					_	-		-	768
	_				gaa Glu				-	-	_	_			_	816
				-	tat Tyr		-		_		_			tga *		861

<210> 204

<211> 286

<212> PRT

<213> Homo sapiens

287

<400> 204 Met Glu Glu Lys Arg Arg Arg Ala Arg Val Gln Gly Ala Trp Ala Ala Pro Val Lys Ser Gln Ala Ile Ala Gln Pro Ala Thr Thr Ala Lys Ser His Leu His Gln Lys Pro Gly Gln Thr Trp Lys Asn Lys Glu His His Leu Ser Asp Arg Glu Phe Val Phe Lys Glu Pro Gln Gln Val Val Arg Arg Ala Pro Glu Pro Arg Val Ile Asp Arg Glu Gly Val Tyr Glu Ile 70 75 Ser Leu Ser Pro Thr Gly Val Ser Arg Val Cys Leu Tyr Pro Gly Phe 90 Val Asp Val Lys Glu Ala Asp Trp Ile Leu Glu Gln Leu Cys Gln Asp 105 100 Val Pro Trp Lys Gln Arg Thr Gly Ile Arg Glu Asp Ile Thr Tyr Gln 120 Gln Pro Arg Leu Thr Ala Trp Tyr Gly Glu Leu Pro Tyr Thr Tyr Ser 135 140 Arg Ile Thr Met Glu Pro Asn Pro His Trp His Pro Val Leu Arg Thr 150 155 Leu Lys Asn Arg Ile Glu Glu Asn Thr Gly His Thr Phe Asn Ser Leu 170 165 Leu Cys Asn Leu Tyr Arg Asn Glu Lys Asp Ser Val Asp Trp His Ser 185 Asp Asp Glu Pro Ser Leu Gly Arg Cys Pro Ile Ile Ala Ser Leu Ser Phe Gly Ala Thr Arg Thr Phe Glu Met Arg Lys Lys Pro Pro Pro Glu Glu Asn Gly Asp Tyr Thr. Tyr Val Glu Arg Val Lys Ile Pro Leu Asp 230 His Gly Thr Leu Leu Ile Met Glu Gly Ala Thr Gln Ala Asp Trp Gln 250 His Arg Val Pro Lys Glu Tyr His Ser Arg Glu Pro Arg Val Asn Leu 265 Thr Phe Arg Thr Val Tyr Pro Asp Pro Arg Gly Ala Pro Trp 275 280

<210> 205

<211> 561

<212> DNA

<213> Homo sapiens

<220>

			CDS (1)	(561)											·
	att		tgg									tta Leu		-		48
			_						_	_		ctt Leu		_		96
												att Ile 45				144
						_	-				_	gag Glu	-			192
	-	-	-		_	_	-		-	-		att Ile				240
			-		-	-				-		att Ile				288
											-	tgc Cys	_	_		336
-		_	_					-		_		gtt Val 125				384
												atg Met		_	_	432
									_		_	tct Ser				480

289

cag gtg ctc cct gtg ttg aaa gag aat gtg gaa ggt cat gat tta cct 528 Gln Val Leu Pro Val Leu Lys Glu Asn Val Glu Gly His Asp Leu Pro 165 170 175 gca tct gag aaa cac cag gat gtt acc tcc taa 561 Ala Ser Glu Lys His Gln Asp Val Thr Ser * 180 185 <210> 206 <211> 186 <212> PRT <213> Homo sapiens <400> 206 Met Ile His Trp His Ser Glu Lys Ala Thr Leu Leu Leu Asn Ala Pro 10 Ser Phe Ser Asp Gln Leu Pro Gly Thr Met Ala Thr Leu Ser Leu Val 25 Asn Glu Ala Gln Tyr Leu Leu Ile Asn Thr Ser Ser Ile Leu Glu Leu His Arg Glm Leu Asn Thr Ser Asp Glu Asn Gly Lys Glu Glu Leu Phe 55 Ser Leu Lys Asp Leu Ser Leu Arg Phe Arg Ala Asn Ile Ile Ile Asn Gly Lys Arg Ala Phe Glu Glu Glu Lys Trp Asp Glu Ile Ser Ile Gly 90 Ser Leu Arg Phe Gln Val Leu Gly Pro Cys His Arg Cys Gln Met Ile 105 Cys Ile Asp Gln Gln Thr Gly Gln Arg Asn Gln His Val Phe Gln Lys 120 Leu Ser Glu Ser Arg Glu Thr Lys Val Asn Phe Gly Met Tyr Leu Met 135 140 His Ala Ser Leu Asp Leu Ser Ser Pro Cys Phe Leu Ser Val Gly Ser 145 150 155 160 Gln Val Leu Pro Val Leu Lys Glu Asn Val Glu Gly His Asp Leu Pro 165 170 Ala Ser Glu Lys His Gln Asp Val Thr Ser 180 185 <210> 207 <211> 1272 <212> DNA <213> Homo sapiens

290

<220> <221> CDS <222> (1)...(1272) <221> misc feature <222> (1)...(1272) <223> n = A,T,C or G<400> 207 atg cac aat tac tgc ttt gtg ttt gct ctg gga tac ctc aca gtg tgc 48 Met His Asn Tyr Cys Phe Val Phe Ala Leu Gly Tyr Leu Thr Val Cys 1 5 10 15 caa gtt act cga gtc tat atc ttt gac tat gga caa tat tct gct gat 96 Gln Val Thr Arg Val Tyr Ile Phe Asp Tyr Gly Gln Tyr Ser Ala Asp 20 25 30 ttt tca ggc cca atg atg atc att act cag aag atc act agt ttg gct 144 Phe Ser Gly Pro Met Met Ile Ile Thr Gln Lys Ile Thr Ser Leu Ala 35 40 tgc gaa att cat gat ggg atg ttt cgg aag gat gaa gaa ctg act tcc 192 Cys Glu Ile His Asp Gly Met Phe Arg Lys Asp Glu Glu Leu Thr Ser 50 55 tca cag agg gat tta gct gta agg cgc atg cca agc tta ctg gag tat 240 Ser Gln Arg Asp Leu Ala Val Arg Arg Met Pro Ser Leu Leu Glu Tyr 65 ttg agt tac aac tgt aac ttc atg ggg atc ctg gca ngc cca ntt tgc 288 Leu Ser Tyr Asn Cys Asn Phe Met Gly Ile Leu Ala Xaa Pro Xaa Cys 85 90 95 tct tac aaa gac tac att act ttc att gaa ggc aga tca tac cat atc 336 Ser Tyr Lys Asp Tyr Ile Thr Phe Ile Glu Gly Arg Ser Tyr His Ile 105 100 110 384 aca caa tot ggt gaa aat gga aaa gaa gag aca cag tat gaa aga aca Thr Gln Ser Gly Glu Asn Gly Lys Glu Glu Thr Gln Tyr Glu Arg Thr 115 125 120 gag cca tct cca aat act gcg gtt gtt cag aag ctc tta gtt tgt ggg 432 Glu Pro Ser Pro Asn Thr Ala Val Val Gln Lys Leu Leu Val Cys Gly

	130					135					140					
_		_				_			-				cct Pro			480
			-					-		-	_		cca Pro		_	528
													aaa Lys 190			576
	-		_		-	-					_	_	ggc Gly			624
	-			_	-			-	-	_		-	tta Leu			672
	_	_						-			-		aag Lys	_		720
													agg Arg			768
	_	-				-				-	-		att Ile 270			816
-					_							-	ttt Phe			864
			_			-	-	_	_	_	-		aac Asn		_	912
													gat Asp			960

305	310		315	320
			tac aca gtt gtg Tyr Thr Val Val	
-			ttt tac agc tcc Phe Tyr Ser Ser 350	• •
· . ·	His Ile Leu G	-	tta ttg ttg ttg Leu Leu Leu Leu . 365	• •
	Gln Arg Arg L	-	gaa aac att cag Glu Asn Ile Gln 380	
			tct ttg gga cag Ser Leu Gly Gln 395	
	-		aat caa gaa ata Asn Gln Glu Ile	•
-	tca cta aag ca Ser Leu Lys G 420			1272
<210> <211> <212> <213>	423			
<222>	VARIANT (1)(423) Xaa = Any Amir	no Acid		·
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Gln	Val	Thr	Arg 20	Val	Tyr	Пe	Phe	Asp 25	Tyr	Gly	Gln	Tyr	Ser 30	Ala	Asp
Phe	Ser	Gly 35	Pro	Met	Met	Пе	Ile 40	Thr	Gln	Lys	Ile	Thr 45	Ser	Leu	Ala
Cys	G1u 50	Ile	His	Asp	Gly	Met 55	Phe	Arg	Lys	Asp	G1u 60	Glu	Leu	Thr	Ser
65			•		70					75				Glu	80
Leu	Ser	Tyr	Asn	Cys 85	Asn	Phe	Met	Gly	Ile 90	Leu	Ala	Xaa	Pro	Xaa 95	Cys
Ser	Tyr	Lys	Asp 100	Tyr	Пe	Thr	Phe	Ile 105	Glu	Gly	Arg	Ser	Tyr 110	His	Ile
Thr	Gln	Ser 115	Gly	Glu	Asn	Gly	Lys 120	Glu	Glu	Thr	Gln	Tyr 125	Glu	Arg	Thr
G1u	Pro 130	Ser	Pro	Asn	Thr	Ala 135	Val	Val	Gln	Lys	Leu 140	Leu	Val	Cys	Gly
Leu 145	Ser	Leu	Leu	Phe	His 150	Leu	Thr	Ile	Cys	Thr 155	Thr	Leu	Pro	Val	Glu 160
Tyr	Asn	Ile	Asp	Glu 165	His	Phe	Gln	Ala	Thr 170	Ala	Ser	Trp	Pro	Thr 175	Lys
He	Пe	Tyr	Leu 180	Tyr	Ile	Ser	Leu	Leu 185	Ala	Ala	Arg	Pro	Lys 190	Tyr	Tyr
Phe	Ala	Trp 195	Thr	Leu	Ala	Asp	Ala 200	Пe	Asn	Asn	Ala	Ala 205	Gly	Phe	Gly
Phe	Arg 210	Gly	Tyr	Asp	Glu	Asn 215	Gly	Ala	Ala	Arg	Trp 220	Asp	Leu	Ile	Ser
Asn 225	Leu	Arg	He	Gln	G1n 230		Glu		Ser	Thr 235	Ser	Phe	Lys	Met	Phe 240
Leu	Asp	Asn	Trp	Asn 245	IJе				Leu 250	Trp	Leu	Lys	Arg	Va1 255	Cys
Tyr	Glu	Arg	Thr 260	Ser	Phe	Ser	Pro	Thr 265	Ile	Gln	Thr	Phe	Ile 270	Leu	Ser
Ala	Пe	Trp 275		Gly	Val	Tyr		Gly	-	Tyr	Leu	Thr 285	Phe	Leu	Thr
Gly	Va1 290	Leu	Met	Thr	Leu	A1a 295	Ala	Arg	Ala	Met	Arg 300	Asn	Asn	Phe	Arg
His 305	Tyr	Phe	He	Glu	Pro 310	Ser	Gln	Leu	Lys	Leu 315	Phe	Tyr	Asp	Val	11e 320
Thr	Trp	Ile	Val	Thr 325	Gln	Val	Ala	Ile	Ser 330	Tyr	Thr	Val	Val	Pro 335	Phe
Val	Leu	Leu	Ser 340		Lys	Pro	Ser	Leu 345		Phe	Tyr	Ser	Ser 350	Trp	Tyr
Tyr	Cys	Leu 355	His	Ile	Leu	Gly	Ile 360	Leu	Val	Leu	Leu	Leu 365		Pro	Val

Lys Lys Thr Gln Arg Arg Lys Asn Thr His Glu Asn Ile Gln Leu Ser 370 375 Gln Ser Lys Lys Phe Asp Glu Gly Glu Asn Ser Leu Gly Gln Asn Ser 395 390 Phe Ser Thr Thr Asn Asn Val Cys Asn Gln Asn Gln Glu Ile Ala Ser 405 410 415 Arg His Ser Ser Leu Lys Gln 420 <210> 209 <211> 1413 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1413) <400> 209 atg tot aga ctg gga gcc ctg ggt ggt gcc cgt gcc ggg ctg gga ctg 48 Met Ser Arg Leu Gly Ala Leu Gly Gly Ala Arg Ala Gly Leu Gly Leu 1 5 15 ttg ctg ggt acc gcc gcc ggc ctt gga ttc ctg tgc ctc ctt tac agc 96 Leu Leu Gly Thr Ala Ala Gly Leu Gly Phe Leu Cys Leu Leu Tyr Ser 20 cag cga tgg aaa cgg acc cag cgt cat ggc cgc agc cag agc ctg ccc 144 Gln Arg Trp Lys Arg Thr Gln Arg His Gly Arg Ser Gln Ser Leu Pro 35 45 aac too otg gac tat acg cag act toa gat occ gga ogc cac gtg atg 192 Asn Ser Leu Asp Tyr Thr Gln Thr Ser Asp Pro Gly Arg His Val Met 50 55 ctc ctg cgg gct gtc cca ggt ggg gct gga gat gcc tca gtg ctg ccc 240 Leu Leu Arg Ala Val Pro Gly Gly Ala Gly Asp Ala Ser Val Leu Pro 65 75 70 80 288 ago ott oca ogg gaa gga oag gag aag gtg otg gac ogc otg gac ttt Ser Leu Pro Arg Glu Gly Gln Glu Lys Val Leu Asp Arg Leu Asp Phe 85 gtg ctg acc agc ctt gtg gcg ctg cgg gag gtg gag gag ctg aga 336

Val	Leu	Thr	Ser 100	Leu	Val	Ala	Leu	Arg 105	Arg	Glu	Val	Glu	Glu 110	Leu	Arg	
						gcg Ala								-	_	384
	_	-			_	aga Arg 135		_			-			-		432
						tcc Ser									-	480
_		_		-	_	ttc Phe		-	-		-	-				528
						tct Ser							_		-	576
						gaa G1u							_	_		624
_	_	-				ttg Leu 215		-		_	-			-		672
-	-					ggt Gly						_		-		720
						gag Glu										768
		Gly				ctg Leu										816
cgg	cag	gac	ttt	ctc	tgg	cgc	ctg	gcc	cga	gcc	tac	agt	gac	atg	tgt	864

Arg	G1n	Asp 275	Phe	Leu	Trp	Arg	Leu 280	Ala	Arg	Ala	Tyr	Ser 285	Asp	Met	Cys	
						agc Ser 295			_			-		-		912
						gct Ala										960
-		-			-	gtg Val		-		-	-	-				1008
				_		cag Gln				_		_				1056
		-		_		cag Gln		_			_	-				1104
						cag Gln 375					-			-		1152
						ctt Leu										1200
						cta Leu										1248
		Ala				tat Tyr	He									1296
	Asn					tgg Trp		_	_	_	Ala	_		_		1344
gat	gtc	acg	aag	gag	gat	ttg	gct	atc	cag	aag	gac	ctg	gaa	gaa	ctg	1392

297

Asp Val Thr Lys Glu Asp Leu Ala Ile Gln Lys Asp Leu Glu Glu Leu 1413 gaa gtc att tta cga gac taa Glu Val Ile Leu Arg Asp * 465 470 <210> 210 <211> 470 <212> PRT <213> Homo sapiens <400> 210 Met Ser Arg Leu Gly Ala Leu Gly Gly Ala Arg Ala Gly Leu Gly Leu 5 Leu Leu Gly Thr Ala Ala Gly Leu Gly Phe Leu Cys Leu Leu Tyr Ser 25 Gln Arg Trp Lys Arg Thr Gln Arg His Gly Arg Ser Gln Ser Leu Pro Asn Ser Leu Asp Tyr Thr Gln Thr Ser Asp Pro Gly Arg His Val Met 55 Leu Leu Arg Ala Val Pro Gly Gly Ala Gly Asp Ala Ser Val Leu Pro Ser Leu Pro Arg Glu Gly Gln Glu Lys Val Leu Asp Arg Leu Asp Phe 90 Val Leu Thr Ser Leu Val Ala Leu Arg Arg Glu Val Glu Glu Leu Arg 105 Ser Ser Leu Arg Gly Leu Ala Gly Glu Ile Val Gly Glu Val Arg Cys 115 120 125 His Met Glu Glu Asn Gln Arg Val Ala Arg Arg Arg Phe Pro Phe 135 140 Val Arg Glu Arg Ser Asp Ser Thr Gly Ser Ser Ser Val Tyr Phe Thr 150 155 Ala Ser Ser Gly Ala Thr Phe Thr Asp Ala Glu Ser Glu Gly Gly Tyr 165 170 Thr Thr Ala Asn Ala Glu Ser Asp Asn Glu Arg Asp Ser Asp Lys Glu 180 185 190 Ser Glu Asp Gly Glu Asp Glu Val Ser Cys Glu Thr Val Lys Met Gly 200 Arg Lys Asp Ser Leu Asp Leu Glu Glu Glu Ala Ala Ser Gly Ala Ser 215 220 Ser Ala Leu Glu Ala Gly Gly Ser Ser Gly Leu Glu Asp Val Leu Pro 225 230 235 240

Leu	Leu	Gln	Gln	A1a 245	Asp	Glu	Leu	His	Arg 250	Gly	Asp	Glu	Gln	G1y 255	Lys		
Arg	Glu	Gly	Phe 260		Leu	Leu	Leu	Asn 265		Lys	Leu	Val	Tyr 270		Ser		
Arg	Gln	Asp 275	Phe	Leu	Trp	Arg	Leu 280	Ala	Arg	Ala	Tyr	Ser 285	Asp	Met	Cys		
Glu	Leu 290	Thr	G1u	Glu	Val	Ser 295	Glu	Lys	Lys	Ser	Tyr 300	Ala	Leu	Asp	Gly		
Lys 305	Glu	Glu	Ala	Glu	Ala 310	Ala	Leu	Glu	Lys	G1y 315	Asp	Glu	Ser	Ala	Asp 320		
Cys	His	Leu	Trp	Tyr 325	Ala	Val	Leu	Cys	G1y 330	Gln	Leu	Ala	Glu	His 335	Glu		
Ser	Ile	Gln	Arg 340	Arg	Пe	Gln	Ser	G1y 345	Phe	Ser	Phe	Lys	G1u 350	His	Val		
Asp	Lys	A1a 355	Пe	Ala	Leu	Gln	Pro 360	Glu	Asn	Pro	Met	A1a 365	His	Phe	Leu		
Leu	G1 <i>y</i> 370	Arg	Trp	Cys	Tyr	G1n 375	Val	Ser	His	Leu	Ser 380	Trp	Leu	Glu	Lys		
Lys 385	Thr	Ala	Thr	Ala	Leu 390	Leu	Glu	Ser	Pro	Leu 395	Ser	Ala	Thr	Val	G1u 400		
	Ala			405				o	410					415			
	Lys		420					425					430				
	Asn	435				·	440		-			445				•	•
•	Va1 450				·	Leu 455	Ala	Ile	Gln	Lys	Asp 460	Leu	Glu	Glu	Leu		
G1u 465	Val	Ile	Leu	Arg	Asp 470												
	<2 <2	212>	1137		oiens	5											
	<2	?20> ?21> ?22>	CDS (1).	(]	137))											
_ 1		00>			- 4	_ 1					_ 4	1		a			40
_	gac Asp				_	_	_		•		_	-		_	-		48

								Leu			aac Asn				96
									_	_	ctc Leu 45			-	144
									-	-	ctg Leu		-	-	192
_	-		 _		_	-	_				acg Thr	-	-	_	240
					_	_		-			gtt Val				288
											tcc Ser				336
											gag Glu 125				384
-					-						atg Met	-		_	432
_	-	-	 	_	_	_	_	_	-	•	acc Thr	_	_	_	480
										_	att Ile		-		528
											atg Met				576

					cgc Arg								624
					gtg Val 215								672
					aat Asn								720
					aag Lys								768
					atc Ile								816
					cag Gln								864
					cca Pro 295								912
					tgg Trp								960
					gtc Val		Met						1008
_	_	-	_		ctc Leu	-						gtt Val	1056
_		_		 -	acg Thr	-		-	-				1104

aac tot gac ago aag cag aaa otg aat gac tga Asn Ser Asp Ser Lys Gln Lys Leu Asn Asp * 370 375 1137

<210> 212 <211> 378 <212> PRT <213> Homo sapiens

<400> 212

Met Asp Leu Ala Gly Leu Leu Lys Ser Gln Phe Leu Cys His Leu Val 10 Phe Cys Tyr Val Phe Ile Ala Ser Gly Leu Ile Ile Asn Thr Ile Gln 25 Leu Phe Thr Leu Leu Leu Trp Pro Ile Asn Lys Gln Leu Phe Arg Lys 40 Ile Asn Cys Arg Leu Ser Tyr Cys Ile Ser Ser Gln Leu Val Met Leu Leu Glu Trp Trp Ser Gly Thr Glu Cys Thr Ile Phe Thr Asp Pro Arg 70 Ala Tyr Leu Lys Tyr Gly Lys Glu Asn Ala Ile Val Val Leu Asn His Lys Phe Glu Ile Asp Phe Leu Cys Gly Trp Ser Leu Ser Glu Arg Phe 105 Gly Leu Leu Gly Gly Ser Lys Val Leu Ala Lys Lys Glu Leu Ala Tyr 120 Val Pro Ile Ile Gly Trp Met Trp Tyr Phe Thr Glu Met Val Phe Cys 135 140 Ser Arg Lys Trp Glu Gln Asp Arg Lys Thr Val Ala Thr Ser Leu Gln 150 155 His Leu Arg Asp Tyr Pro Glu Lys Tyr Phe Phe Leu Ile His Cys Glu 165 170 Gly Thr Arg Phe Thr Glu Lys Lys His Glu Ile Ser Met Gln Val Ala 185 Arg Ala Lys Gly Leu Pro Arg Leu Lys His His Leu Leu Pro Arg Thr 195 200 205 Lys Gly Phe Ala Ile Thr Val Arg Ser Leu Arg Asn Val Val Ser Ala 215 220 Val Tyr Asp Cys Thr Leu Asn Phe Arg Asn Asn Glu Asn Pro Thr Leu 230 235 Leu Gly Val Leu Asn Gly Lys Lys Tyr His Ala Asp Leu Tyr Val Arg 245 250

Arg	Ile	Pro	Leu 260	Glu	Asp	Ile	Pro	G1u 265	Asp	Asp	Asp	Glu	Cys 270	Ser	Ala	
Trp	Leu	His 275	Lys	Leu	Tyr	Gln	G1u 280	Lys	Asp	Ala	Phe	G1n 285	Glu	Glu	Tyr	
Tyr	Arg 290	Thr	Gly	Thr	Phe	Pro 295	Glu	Thr	Pro	Met	Val 300		Pro	Arg	Arg	
Pro 305	Trp	Thr	Leu	Val	Asn 310	Trp	Leu	Phe	Trp	Ala 315		Leu	۷a٦	Leu	Tyr 320	
Pro	Phe	Phe	Gln	Phe 325	Leu	Val	Ser	Met	Ile 330	Arg	Ser	Gly	Ser	Ser 335	Leu	
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G1n gaa	gcg Ala	gcc Ala 35	20 cac His	tgg Trp ccc	cag	ttc Phe agc	gag Glu 40 cac	25 acc Thr	gcg Ala	ctg Leu cac	agc Ser cag	acg Thr 45	30 . ttc Phe	ttc Phe tgc	caa Gln act	144 192

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-	ggc Gly			tga *												495
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Gln	Ala	Ala 35		Trp	Gln	Phe	Glu 40		Ala	Leu	Ser	Thr 45		Phe	Gln	
Glu	Thr 50		Пe	Pro	Asn	Ser 55	. •	His	His	His	Gln 60		Met	Cys	Thr	
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Ser	Pro 130	Thr	Thr	Phe	His	His 135	Leu	His	Arg	Pro	Gln 140	Pro	Thr	Trp	Pro	
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			ctc Leu													192
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						-		_		-			-	cac His		672
		-		_	-	_		_		_			_	gag G1u	_	720
			_	_			-	_	-	_	-			ctg Leu 255	-	768
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Phe	Asp	Gly	Asp 260	Asp	Leu	Leu	Glu	Thr 265	Gly	Lys	Asn	Val	Lys 270	Ile	Thr	
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			-	-	gga Gly 390							-	-	-	-	1200
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		_	_	-	cct Pro		_									1296
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					aga Arg											1776
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Lys	Met 610	Lys	Glu	Gln	Arg	Leu 615	Arg	Glu	His	Leu	Va1 620	Arg	Phe	Glu	Arg	
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					aat Asn											2496
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					aga Arg											2592
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	-		_		cct Pro			-	_	-						2784
_	-			_	aga Arg											2832
_				-	gag Glu 950	-			-	_						2880
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Glu	Leu	Lys 35	Arg	Arg	Asn	Leu	Asp 40	Ile	Thr	Gly	Val	Lys 45	Thr	Va1	Leu	
Ile	Ser 50	Arg	Leu	Lys	Gln	A1a 55	Пe	Glu	Glu	Glu	G1 <i>y</i> 60	Gly	Asp	Pro	Asp	
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Ser	Lys 210	Pro	Leu	Pro	Ser	Glu 215	Gly	Ser	Leu	Ala	G1u 220	Ala	Asp	His	Thr
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•		275			•		Lys 280	,			·	285			
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G1u 545	Lys	Lys	Arg	Ile	Ser 550	Ser	Lys	Ser	Pro	Gly 555	His	Met	Val	Ile	Leu 560
·			-	565	·				Pro 570			_		575	-
	-		580				-	585	Lys				590		·
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•	610	·			•	615			His		620	_			_
625	•	_			630		_		Arg	635					640
	Ū	Ĭ		645					11e 650		_			655	
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	690					695			Glu		700				
705					710				Gln	715					720
•	•			725			-		Arg 730			·		735	
•	·		740	·				745	Lys				750		·
Ąla	Arg	Phe 755	-	His	Gly	Ser	-	Tyr	Ser	Arg	Gln	G1n 765	Asn	Arg	Phe
Asn	Asp 770	Phe	Asp	His	Arg	G1u 775	Arg	Gly	Arg	Phe	Pro 780	Glu	Ser	Ser	Ala
Va1 785	Gln	Ser	Ser	Ser	Phe 790	Glu	Arg	Arg	Asp	Arg 795	Phe	Val	Gly	Gln	Ser 800
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Ser	Arg 930	G1u	Gly	Asp	Arg	G1 <i>y</i> 935	Val	Ile	Thr	Asp	Arg 940	Gly	Gly	Gly	Ser	
G1n 945	His	Tyr	Pro	Glu	G1u 950	Arg	His	Val	Val	G1u 955	Arg	His	Gly	Arg	Asp 960	
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-		-				cga Arg 135	_							-	-	2	432
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-	-		_			gag Glu		-					-	-		Ę	576
-	-	-				gat Asp	-									e	524
cta	ttg	tca	gat	gaa	gac	tgt	atg	tct	gtg	ссс	gga	aaa	act	cac	aga	6	572

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		•	-					_						gat Asp	•	816
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		-		-									-	gaa Glu 335	_	1008
		_	_		-	-	_			-		-	-	gaa Glu		1056
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Tyr			_					-						gga Gly		1152
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Glu	G1u 50		Arg	Ala	Glu	G1n 55	Arg	Lys	Tyr	Gly	Va1 60	Phe	Phe	Asp	Asp	
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PCT/US00/29052

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Asp	Asp	Phe	Ile	Leu 165	Gln	Ala	Asn	Lys	Ala 170	Thr	Gly	Glu	Glu	G1u 175	Gly
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	210		•		Asp	215					220				
225			•		Leu 230		·			235		-		•	240
		•		245	Thr				250					255	
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		435			Arg		440					445			
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25
30

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Trp	Thr	I le 35	Val	Gly	Val	Ala	A1a 40	Leu	Ile	Leu	Phe	Leu 45	Val	Ala	Leu
Leu	A1 a 50	Arg	Val	Leu	Val	Lys 55	Arg	Lys	Pro	Pro	Arg 60	Asp	Pro	Leu	Phe
Tyr 65	Val	Tyr	Ala	Val	Phe 70	Gly	Phe	Thr	Ser	Va1 75	۷a۱	Asn	Leu	He	Ile 80
Gly	Leu	Glu	Gln	Asp 85	Gly	Пe	Ile	Asp	Gly 90	Phe	Met	Thr	His	Tyr 95	Leu
Arg	Glu	Gly	Glu 100	Pro	Tyr	Leu	Asn	Thr 105	Ala	Tyr	Gly	His	Met 110	Пе	Cys
Tyr	Trp	Asp 115	Gly	Ser	Ala	His	Tyr 120	Leu	Met	Tyr	Leu	Val 125	Met	Val	Ala
Ala	Ile 130	Ala	Trp	Glu	Glu	Thr 135	Tyr	Arg	Thr	Ile	Gly 140	Leu	Tyr	Trp	Val
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Gly	Lys	Tyr	Gly	Thr 165	Arg	Ile	Cys	Pro	Ala 170	Phe	Phe	Leu	Ser	I 1e 175	Pro
Tyr	Thr	Cys	Leu 180	Pro	Val	Trp	Ala	Gly 185	Phe	Arg	Ile	Tyr	Asn 190	Gln	Pro
Ser	Glu	Asn 195	Tyr	Asn	Tyr	Pro	Ser 200	Lys	Val	He	Gln	G1u 205	Ala	Gln	Ala
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Cys	Pro	Ser	Glu	Leu 245	Cys	Arg	Leu	Tyr	Thr 250	Gln	Phe	Gln	Glu	Pro 255	Tyr
Leu	Lys	Asp	Pro 260	Ala	Ala	Tyr		Lys 265	Ile	Gln	Met	Leu	Ala 270	Tyr	Met
Phe	Tyr	Ser 275	Val	Pro	Tyr	Phe	Val 280	Thr	Ala	Leu	Tyr	G1y 285	Leu	Val	۷a۱
Pro	G1 <i>y</i> 290	Cys	Ser	Trp	Met	Pro 295	Asp	Ile	Thr	Leu	Ile 300	His	Ala	Gly	Gly
Leu 305	Ala	Gln	Ala	Gln	Phe 310	Ser	His	Ile	Gly	A1a 315	Ser	Leu	His	Ala	Arg 320
	Ala	Tyr	Val	Луг 325		Val	Pro	Glu	G1u 330	Ala	Lys	Ile	Leu	Phe 335	Leu
Ala	Leu	Asn	11e 340		Tyr	Gly	Val	Leu 345		Gln	Leu	Leu	A1a 350	Tyr	Arg

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Leu Thr Leu Ile Lys Gln His Gln Glu Leu Ile Leu Glu Ala Thr Ser
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Val Pro Asp Ile Cys Asp Lys Phe Lys Gln Ile Thr Lys Gly Ser Phe
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                                        75
Val Met Glu Cys His Thr Phe Met Gln Lys Ile Phe Ser Glu Pro Gly
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tgg gcc tcc gtg agc gcc cag acc gat gcc acc ccg gcg gtg acg aca
Trp Ala Ser Val Ser Ala Gln Thr Asp Ala Thr Pro Ala Val Thr Thr
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										_		cca Pro 60						192
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												tgc Cys	_	-		-		288
	-	-			_		_	_			_	tgc Cys		-		_		336
•	-	-		_	-	-		-	-			gca Ala	_				;	384
	-				-					-	-	ttt Phe 140	_		_	_	•	432
	-							-				aca Thr					•	480
	-							-	_		_	gaa Glu				_	;	528
		-	-				-				-	aat Asn	-	_			ţ	576
												gct Ala	_				(524

			cct Pro												672
	Leu		tca Ser		_	_		_			•	• •		_	720
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-	-		gaa G1u 260	_		-	_	-		_	_	•	•		816
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	-		cag Gln					_		_			~		912
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ctc (Leu F								13	392
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agg a Arg l								1!	536
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gta a								10	632
aat g Asn (545								1	680

tot goa cot goa gag goa ggo tto aga got coa coa goo ato aat goo 1728 Ser Ala Pro Ala Glu Ala Gly Phe Arg Ala Pro Pro Ala Ile Asn Ala 565 570 575 1764 agg ctg ccc ttt aac ttc ttc ttc ccg ttt gtt tga Arg Leu Pro Phe Asn Phe Phe Phe Pro Phe Val * 580 585 <210> 226 <211> 587 <212> PRT <213> Homo sapiens <400> 226 Met Arg Pro Arg Gly Leu Pro Pro Leu Leu Val Val Leu Leu Gly Cys 10 Trp Ala Ser Val Ser Ala Gln Thr Asp Ala Thr Pro Ala Val Thr Thr Glu Gly Leu Asn Ser Thr Glu Ala Ala Leu Ala Thr Phe Gly Thr Phe 40 Pro Ser Thr Arg Pro Pro Gly Thr Pro Arg Ala Pro Gly Pro Ser Ser 55 Gly Pro Arg Pro Thr Pro Val Thr Asp Val Ala Val Leu Cys Val Cys 70 75 Asp Leu Ser Pro Ala Gln Cys Asp Ile Asn Cys Cys Cys Asp Pro Asp 90 Cys Ser Ser Val Asp Phe Ser Val Phe Ser Ala Cys Ser Val Pro Val 105 Val Thr Gly Asp Ser Gln Phe Cys Ser Gln Lys Ala Val Ile Tyr Ser 120 Leu Asn Phe Thr Ala Asn Pro Pro Gln Arg Val Phe Glu Leu Val Asp 135 Gln Ile Asn Pro Ser Ile Phe Cys Ile His Ile Thr Asn Tyr Lys Pro 150 155 Ala Leu Ser Phe Ile Asn Pro Glu Val Pro Asp Glu Asn Asn Phe Asp 170 165 Thr Leu Met Lys Thr Ser Asp Gly Phe Thr Leu Asn Ala Glu Ser Tyr 180 185 Val Ser Phe Thr Thr Lys Leu Asp Ile Pro Thr Ala Ala Lys Tyr Glu 200 Tyr Gly .Val Pro Leu Gln Thr Ser Asp Ser Phe Leu Arg Phe Pro Ser 210 215 220

Ser 225	Leu	Thr	Ser	Ser	Leu 230	Cys	Thr	Asp	Asn	Asn 235	Pro	Ala	Ala	Phe	Leu 240
	Asn	Gln	Ala	Va1 245		Cys	Thr	Arg	Lys 250	Ile	Asn	Leu	Glu	G1n 255	Cys
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	290		Gln			295					300				
305			Gln		310					315					320
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			Thr	405				•	410					415	
			Asp 420					425					430		
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465			Pro		470					475					480
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Val	Thr 530	Ala	Asn	Leu	Пe	Ser 535	Ser	Ser	Phe	Pro	G1u 540	Ala	Asn	Ser	Gly
Asn 545	Glu	Arg	Thr	Пe	Leu 550	Пe	Ser	Thr	Ala	Va1 555		Phe	Val	Asp	Val 560
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Leu 225	Val	Ala	Asn	Val	Ala 230	Пe	Gly	Leu	Val	Asn 235	Val	Val	Trp	Trp	Leu 240	
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Val	Val	Val	Va1 260	Leu	Leu	Leu	Gln	Gly 265	Leu	Ser	Leu	Leu	G1u 270	Leu	Leu ·	
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Пe	Ser 290		Ile	Pro	Val	His 295	Val	Leu	Phe	Phe	Ser 300	Phe	Leu	Glu	Asp	
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334

Leu 65	Gln	Leu	Leu	Gly	Arg 70	Leu	Pro	Leu	Phe	Gly 75	Leu	Gly	Arg	Leu	Va1 80	
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	_				ccc Pro										-	336
_	_				ctg Leu					-					_	384
					gtc Val											432
					ttc Phe 150											480
_	-			_	tac Tyr	_					_					528
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Arg Leu Pro Val Arg Ala Trp Ala Asp Val Arg Arg Glu Xaa Arg Leu
Leu Gln Leu Leu Gly Arg Leu Pro Leu Phe Gly Leu Gly Arg Leu Val
                    70
                                        75
Thr Arg Lys Ser Trp Leu Trp Gln His Asp Glu Pro Cys Tyr Trp Arg
                                    90
Leu Thr Arg Val Arg Pro Asp Tyr Thr Ala Gln Asn Leu Asp His Gly
                                105
Lys Ala Trp Gly Ile Leu Thr Phe Lys Gly Lys Thr Glu Ser Glu Ala
                            120
Arg Glu Ile Glu His Val Met Tyr His Asp Trp Arg Leu Val Pro Lys
                        135
                                            140
His Glu Glu Glu Ala Phe Thr Ala Phe Thr Pro Ala Pro Glu Asp Ser
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Leu Ala Ser Val Pro Tyr Pro Pro Leu Leu Arg Ala Met Ile Ile Ala
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Glu Arg Gln Lys Asn Gly Asp Thr Ser Thr Glu Glu Pro Met Leu Asn
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cac atg ccc at His Met Pro I		_			_
gtc acc cag ti Val Thr Gln Ph 65					
ccc gag tcc ct Pro Glu Ser Le	•		-		-
ata ccg tat th Ile Pro Tyr Ph 10		_		_	
aca gtg ggc ca Thr Val Gly Hi 115					
gct cca gat aa Ala Pro Asp As 130	sn Phe Āsp G				
tct caa gaa ta Ser Gln Glu Ty					

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cca gca gtg aca g Pro Ala Val Thr A 10	p Asn Asp Glu		
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aag ccc gtc acc to Lys Pro Val Thr Cy 195			
gat gcg gac att ca Asp Ala Asp Ile H ¹ 210	_		
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agg ctg aag gtg ta Arg Leu Lys Val Ty 24	r Lys Leu Lys		
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gaa ctg ggc atc at Glu Leu Gly Ile Il 290			
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338

325 330 335 1056 cag gag gag agc gcc gag cgg agn agg ccc tca cag cat gtg gtg ctc Gln Glu Glu Ser Ala Glu Arg Xaa Arg Pro Ser Gln His Val Val Leu ago ctg act ttc aag cgt tat gtc ttc gac acc cac aag cgc atg gtt 1104 Ser Leu Thr Phe Lys Arg Tyr Val Phe Asp Thr His Lys Arg Met Val 355 360 365 cag tct ccc tga 1116 Gln Ser Pro * 370 <210> 232 <211> 371 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(371) <223> Xaa = Any Amino Acid <400> 232 Met Ser Val Ala His Cys Phe Ser Ile Lys Gly Gln Gly Thr Val Met Thr Gly Thr Ile Leu Ser Gly Ser Ile Ser Leu Gly Asp Ser Val Glu . 25 Ile Pro Ala Leu Lys Val Val Lys Lys Val Lys Ser Met Gln Met Phe 40 His Met Pro Ile Thr Ser Ala Met Gln Gly Asp Arg Leu Gly Ile Cys 55 Val Thr Gln Phe Asp Pro Lys Leu Leu Glu Arg Gly Leu Val Cys Ala 70 75 Pro Glu Ser Leu His Thr Val His Ala Ala Leu Ile Ser Val Glu Lys 90 Ile Pro Tyr Phe Arg Gly Pro Leu Gln Thr Lys Ala Lys Phe His Ile 105 Thr Val Gly His Glu Thr Val Met Gly Arg Leu Met Phe Phe Ser Pro 120 Ala Pro Asp Asn Phe Asp Gln Glu Pro Ile Leu Asp Ser Phe Asn Phe 130 135 140

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Pro	Ala	Val	Thr	Asp 165		Asp	Glu	Ala	Asp 170	Lys	Lys	Ala	Gly	G]n 175	
Thr	Glu	Gly	His 180		Pro	Arg	Gln	Gln 185	Trp	Ala	Leu	Val	Glu 190		Glu
Lys	Pro	Val 195	Thr	Cys	Pro	Arg	Leu 200	Cys	Leu	Val	Ile	Gly 205		Arg	Leu
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	•		Lys	325					330					335	_
			Ser 340					345					350		
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_	-	-			gct Ala									384
					ctt Leu									432
-					aaa Lys 150			-						480
					tta Leu									528

		_				tat Tyr						_	_			576
			_			aat Asn										624
						gta Val 215	-		_		_					672
	_	-		_		atc Ile	_						_			720
-					-	aaa Lys		_	-				-			768
						cct Pro			-				-	_		816
-					-	cac His	-			-				-		864
_			-	-		tct Ser 295			-	-				_		912
						aaa Lys										960
						ctg Leu										1008
		Pro				gat Asp									-	1056

													gtc Val			1104
	-						_						cga Arg			1152
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1				5		Ť	_		10				Thr	15		
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He	A1a 50	Gly	ınr	Arg	PIU		vui	AI 9	ווכת	uij	60		LCU		00,	
	50					55					60		Leu			

				0.5					90					95	
1	1	DI	1	85	DI	1	47.	01		77.	V-7	۸	61.4		Th.
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Asp 145		Tyr	Asn	His	Lys 150		Pro	Glu	Ser	Asn 155		Lys	Met	Lys	Ile 160
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Thr 225	Lys	Leu	Leu	Gln	Phe 230	Пe	Gln	Asn	Ile	Ile 235	Tyr	Glu	Glu	Gly	Phe 240
Asp	Gly	Ser	Asn	Pro 245	Gln	Lys	Lys	Gln	Arg 250	Asn	Ile	Leu	Arg	I1e 255	Gly
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aac a Asn S 145															480
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gtg (576
gtc a Val S	-	_	-	-	-	_		_				-		-	624
ata 1 Ile 8			_								_	_	_	 _	672
ctt (Leu / 225	-	-	_			_									720
aac d Asn l															768
gtg (Val /	_					_		-		_			_	 _	816
ctc (Leu l															864
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gga (Gly (_					-				-	-		-		960

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Ser	Leu 50		Ala	Val	Glu	Arg 55	-	Pro	Glu	Glu	G1n 60		Пе	Ala	Met	•	
Va1 65		Asn	Leu	Leu	A1a 70		Tyr	Glu	Gln	Arg 75		Trp	Ala	Gln	Thr 80		
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Tyr	Thr	Arg	Leu 100		His	Leu	Leu	Lys 105		Lys	Leu	Glu	Asp 110		Asn		
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Met	He	Gln	Glu	11e 165	Gln	Gln	Ala	Ala	G1u 170	Arg	Leu	Glu	Arg	Asn 175	Phe
۷a۱	Asp	Ser	Arg 180	Gln	Leu	Lys	Val	Cys 185	Ala	Thr	Cys	Phe	Asp 190	Leu	Ser
Val	Ser	Leu 195		Arg	Val	Leu	Glu 200	Met	Thr	Ile	Thr	Leu 205		Pro	Glu
Ile	Phe 210		Asp	Trp	.Thr	Arg 215		Thr	Ser	Glu	Met 220		Leu	Arg	Arg
Leu 225		Gln	Leu	Leu	Asn 230		Val	Leu	Asn	Arg 235		Thr	Ala	Glu	Arg 240
	Leu	Phe	Asp	Arg 245		Val	Thr	Leu	Arg 250		Pro	Gly	Leu	G1u 255	
Val	Asp	His	Tyr 260		Пe	Leu	۷al	A1 a 265		Thr	G1y	Ile	Leu 270	Val	Gln
Leu	Leu	Val 275		Gly	Pro	Ala	Ser 280		Arg	Glu	Gln	A1a 285		Ser	Val
Leu	Leu 290		Asp	Pro	Cys	Phe 295		Leu	Arg	Ser	Ile 300		Tyr	Leu	Leu
G1y 305		Pro	Glu	Pro	Pro 310		Pro	Gly	Thr	Ala 315		Pro	Ala	Pro	Asp 320
	Lys	Arg	Phe	Ser 325		G1n	Ser	Tyr	A1a 330	Asp	Tyr	Ile	Ser	A1a 335	
Glu	Leu	Ala	G1n 340	Val	Glu	Gln	Met	Leu 345		His	Leu	Thr	Ser 350	Ala	Ser
Ala	Gln	A1 a 355	Ala	Ala	Ala	Ser	Leu 360	Pro	Thr	Ser	Glu	G1u 365		Ser	Ala
Pro	Ser 370		Met	Pro	Thr	Pro 375	Ser	Leu	Leu	Cys	Ser 380	Ser	Pro	Val	Ala
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							cta Leu								528
							gcc Ala 185								576
		-	_			-	cta Leu	-				•	~		624
							gat Asp								672
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							att Ile			-		_			768
	-				_		tca Ser 265				-				816
							cgt Arg	-	_		_				864
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350

325 330 335 agt ggt aaa tgc cct ctt cca agg caa caa gta aca gaa att ata ttt 1056 Ser Gly Lys Cys Pro Leu Pro Arg Gln Gln Val Thr Glu Ile Ile Phe 345 340 350 gtt tta aaa gca gtc agt act ctt att gat tca ctt aag aaa act cag 1104 Val Leu Lys Ala Val Ser Thr Leu Ile Asp Ser Leu Lys Lys Thr Gln 355 360 365 cct gag aat gtt gat gga aat acc tgg gca caa gta att gcc tta tac 1152 Pro Glu Asn Val Asp Gly Asn Thr Trp Ala Gln Val Ile Ala Leu Tyr 370 375 cca act tta gta gaa tgc atc acc tgt tct tct tca gaa gtc tgt tct 1200 Pro Thr Leu Val Glu Cys Ile Thr Cys Ser Ser Ser Glu Val Cys Ser 385 390 395 400 gca ctt aaa gag gca cta gtt cct ttt aag gat ttc atg cag cca cca 1248 Ala Leu Lys Glu Ala Leu Val Pro Phe Lys Asp Phe Met Gln Pro Pro 410 gca tcc aga gtt caa aat gga gaa tct tga 1278 Ala Ser Arg Val Gln Asn Gly Glu Ser * 420 425 <210> 238 <211> 425 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(425) <223> Xaa = Any Amino Acid <400> 238 Met Asp Asp Leu Gln Lys Leu Gly Val Ile Leu His Ser Ala Ile Ser 10 Val Pro Ile Ser Ser Asp Ala Ser Pro Phe Ile Leu Pro Ser Tyr Thr 25 Glu Ala Val Leu Thr Ser Leu Gln Glu Ala Val Leu Thr Ala Leu Asp 35 40 45

Val	Leu 50	Gln	Lys	Ala	He	Cys 55	Val	Gly	Pro	Glu	Asn 60	Met	Gln	Ile	Met
Tyr 65	Pro	Ala	Ile	Phe	Asp 70	Gln	Leu	Leu	Ala	Phe 75	Val	Glu	Phe	Ser	Cys 80
Lys	Pro	Pro	Gln	Tyr 85	Gly	Gln	Xaa	Glu	Thr 90	Lys	His	Ile	Ala	Asn 95	Ala
Lys	Tyr	Asn	Gln 100	Пе	Gln	Leu	Phe	Ala 105	Pro	Ala	Glu	Trp	Val 110	Ala	Leu
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-	130					135	Lys				140				
145				-	150		Arg			155				-	160
				165			Lys		170					175	
			180	•			Val	185	Ū				190		_
•		195			·		G1u 200					205		·	
	210					215	Pro	·			220				
225					230	·	Val			235					240
				245			Phe		250					255	
			260			-	Gly	265					270		
		275				·	Ile 280	_				285			
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Thr 305	Pro	Gln	Glu	Gly			Ser					Ser	Val	Leu	Leu 320
Lys	Arg	Ser	Gln	Asp 325	Val	Leu	His	Arg	Tyr 330	Пe	Glu	Asp	Glu	Arg 335	Leu
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Val	Leu	Lys 355	Ala	Val	Ser	Thr	Leu 360	He	Asp	Ser	Leu	Lys 365	Lys	Thr	Gln
Pro	G1u 370	Asn	Val	Asp	Gly	Asn 375	Thr	Trp	Ala	G1n	Val 380	Пe	Ala	Leu	Tyr
Pro 385	Thr	Leu	Val	Glu	Cys 390	Ile	Thr	Cys	Ser	Ser 395	Ser	Glu	Val	Cys	Ser 400

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								ttc Phe								144
								aag Lys								192
		_				_		atg Met	-	-						240
								gct Ala								288
					-		-	gct Ala 105			-		-			336
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WO 01/29221

353

PCT/US00/29052

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	-					-	_	-		-	atg Met		-			480
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	-						-		-		cag Gln	_	-	_	-	576
_		-	-								ctt Leu		_	-	_	624
-		_		-		_		_			cat His 220			-		672
		•		_	-	-		-		_	gca Ala		_		•	720
-			-	His		Lys	Leu	Ser		Ile	cgc Arg		-			768
					_			-			gtg Val		_	_	_	816
											gct Ala					864
aca	aat	nan	ato	tcc	cat	cat	gat	act	tta	nat	act	act	tcc	caa	uua	912

Thr	Gly 290	Glu	Met	Ser	His	His 295	Asp	Thr	Leu	Asp	A1a 300	Ala	Ser	Gln	Gly	
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	Phe	Ala			Trp	Asp	Asn			Leu	Leu	Val		15 Pro	Ser	
Ser		His	20	Ser	•		Leu	25	Gly			Asp	30			
Ser Pro	Pro Val	His 35	20 Thr	Ser Val	Asn	Thr Leu	Leu 40	25 Phe	Gly Leu	Thr	Asn Asp	Asp 45	30 Leu	Pro	Glu	
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Ser Pro Glu Tyr 65 Trp	Pro Val 50 His Lys Ser	His 35 Met Pro Glu Pro	20 Thr Glu Pro Arg His 100	Ser Val Glu Ile Leu 85 Thr	Asn Val Phe 70 Val	Thr Leu 55 Arg Ile Tyr	Leu 40 Gln Pro Arg Asp	25 Phe Lys Met Ala Ala 105	Gly Leu Lys Lys Leu 90 Ala	Thr Ala Arg 75 Glu Pro	Asn Asp 60 Ile Asn Gln	Asp 45 Leu Thr Arg Gly Pro	30 Leu Ile Trp Val Val 110	Pro Thr Leu Asn Gly 95	Glu Ser Thr 80 Ile Asn	
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Ser Pro Glu Tyr 65 Trp Tyr Trp Ser	Pro Val 50 His Lys Ser Leu Lys 130	His 35 Met Pro Glu Pro Ala 115 Ala	20 Thr Glu Pro Arg His 100 Lys	Ser Val Glu Ile Leu 85 Thr Gly Asn	Asn Val Phe 70 Val Ala Leu Tyr	Thr Leu 55 Arg Ile Tyr Gly Pro 135	Leu 40 Gln Pro Arg Asp Ala 120 Thr	25 Phe Lys Met Ala Ala 105 Cys	Gly Leu Lys Lys Leu 90 Ala Thr	Thr Ala Arg 75 Glu Pro Ser Asn	Asn Asp 60 Ile Asn Gln Arg His 140	Asp 45 Leu Thr Arg Gly Pro 125 Arg	30 Leu Ile Trp Val Val 110 Ile Val	Pro Thr Leu Asn Gly 95 Asn His	Glu Ser Thr 80 Ile Asn Pro	

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Gln	Val	Val 195	Asp	Phe	Leu	Ser	Arg 200	Asn	Lys	Gln	Leu	Tyr 205	Gln	Lys	Thr	
Glu	Ile 210		Ser	Leu	Glu	Lys 215		Leu	Leu	Leu	His 220		Gly	Met	Gly	
Arg 225	Leu	Cys	Thr	Leu	Asp 230		Ser	Val	Ser	Leu 235		Thr	Met	Ile	Asp 240	
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Val	Gly	Arg	Thr 260	Leu	Glu	Ser	Gln	Val 265	Lys	Val	Val	Ala	Leu 270	Cys	Ala	
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	-	-	-										ggc Gly			144

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						ggt Gly										528
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						cac His										•	864
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Gln	Val	Va1 35	Val	Glu	Ser	Leu	Tyr 40	Пе	Ile	Ser	Cys	Tyr 45	Gly	Thr	Leu		
Val	G1u 50	His	Met	Met	Glu	Pro 55	Arg	Pro	Leu	Ser	Thr 60	Ala	Pro	Lys	Ile		
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Phe Leu Leu Ala Gly Leu Val Pro Pro Gly Ser Pro Gly Pro Ile Thr
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Arg His Gly Ser Tyr Asp Ser Leu Ala Ser Asp His Ser Gly Gln Glu
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Asp Glu Glu Trp Leu Ser Gln Val Glu Ile Val Thr His Thr Gly Pro
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                                                            160
His Arg Arg Leu Trp Met Gly Pro Gln Phe Gln Phe Lys Thr Ile His
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Pro Ser Gly Gln Thr Thr Val Ile Ser Ser Ser Ser Val Leu Gln
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Ser His Gly Pro Ser Asp Thr Pro Gln Pro Leu Leu Asp Phe Asp Thr
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Asp Asp Leu Asp Leu Asn Ser Leu Arg Ile Gln Pro Val Arg Ser Asp
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Pro Val Ser Met Pro Gly Ser Ser Arg Pro Val Ser Asp Arg Arg Gly
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Val Ser Thr Val Ile Asp Ala Ala Ser Gly Thr Phe Asp Arg Ser Val
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Gly Arg Leu Gly Ser Pro Lys Pro Glu Arg Gln Arg Gly Gln Asn Ser
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Lys Ala Pro Ala Ala Pro Ala Asp Arg Lys Arg Xaa Xaa Ser Pro Gln
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Gly	Asp	Tyr	Asn 340	Met	Asp	Gly	Tyr	Pro 345	Asp	Ala	Leu	Val	11e 350	Leu	Lys
Asn	Thr	Ser 355	Gly	Ser	Asn	Gln	G1n 360	Ala	Phe	Leu	Leu	G1u 365	Asn	Val	Pro
Cys	Asn 370	Asn	Ala	Ser	Cys	G1u 375	Glu	Ala	Arg	Arg	Met 380	Phe	Lys	Val	Tyr
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Phe	Phe	Asp	He	Tyr 405	Glu	Asp	Gly	Ile	Leu 410	Asp	Ile	Val	Val	Leu 415	Ser
Lys	Gly	Tyr	Thr 420	Lys	Asn	Asp	Phe	Ala 425	IJе	His	Thr	Leu	Lys 430	Asn	Asn
Phe	Glu	A1 a 435	Asp	Ala	Tyr	Phe	Val 440	Lys	Val	He	Val	Leu 445	Ser	Gly	Leu
Cys	Ser 450	Asn	Asp	Cys	Pro	Arg 455	Lys	Ile	Thr	Pro	Phe 460	Gly	Val	Asn	Gln
Pro 465	Gly	Pro	Tyr	Пe	Met 470	Tyr	Thr	Thr	Val	Asp 475	Ala	Asn	Gly	Tyr	Leu 480
Lys	Asn	Gly	Ser	A1a 485	Gly	Gln	Leu	Ser	G1n 490	Ser	Ala	His	Leu	A1a 495	Leu
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Arg	Lys 530	Gln	Glu	Trp	Thr	A7a 535	Ile	Ile	Pro	Asn	Ser 540	Gln	Leu	Пe	Val	
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-	-	-	-			aaa Lys	-			_	-					240

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-			tcc Ser	-			-			-				-	-	240
			tat Tyr													288

							atg Met 105								336
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_				-			cag G1n	_		-	_				528
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							acg Thr								624
	-					-	agg Arg			-	_	-		-	672
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	_		-				atc Ile								768
-							999 G1y 265								816

	gaa Glu	-														864
•	atc Ile 290															912
	ccc Pro	-			,											960
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			20					25					30			
•	His	35					40			-	•	45				
Cys	Va1 50	Thr	Gln	Phe	Asp	Pro 55	Lys	Leu	Leu	Glu	Arg 60	Gly	Leu	Val	Cys	

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Ile	Thr	Val	Gly 100	His	Glu	Thr	Val	Met 105	Gly	Arg	Leu	Met	Phe 110	Phe	Ser
Pro	Ala	Pro 115	Asp	Asn	Phe	Asp	Gln 120	Glu	Pro	Tle	Leu	Asp 125	Ser	Phe	Asn
Phe	Ser 130	Gln	Glu	Tyr	Leu	Phe 135	Gln	Glu	Gln	Tyr	Leu 140	Ser	Lys	Asp	Leu
Thr 145	Pro	Ala	Val	Thr	Asp 150	Asn	Asp	Glu	Ala	Asp 155	Lys	Lys	Ala	Gly	Gln 160
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Leu	Asp	Ala 195	Asp	Ile	His	Thr	Asn 200	Thr	Cys	Arg	Leu	A1a 205	Phe	His	Gly
He	Leu 210	Leu	His	Gly	Leu	G1u 215	Asp	Arg	Asn	Tyr	A1a 220	Asp	Ser	Phe	Leu
225			_		230			_		235			Leu		240
Arg	Ala	Met	Asp	Asp 245	Tyr	Ser	Val	He	G1y 250	Arg	Ser	Leu	Phe	Lys 255	Lys
			260					265		-			Leu 270		
		275	_			•	280			-		285	Gly	•	
	290				_	295					300	-	Lys		
305				•	310	_		_		315	_	-	Glu		Thr 320
Arg	Gln	Glu	Glu	Ser 325	Ala	Glu	Arg	Xaa	Xaa 330	Pro	Ser	Gln	His	Va1 335	Val
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			999 Gly 70								240
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			cat His								384
			tgg Trp								432
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-	gaa G1u				-			-	-		_				240	
	ccg Pro	-			-	-	-	-		_		_	-		288	
	cag Gln				_			-				-	_		336	
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Ala Ala Gly Gly Ala Ala Thr Lys Lys Pro Lys Lys Glu Leu Lys
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Gly Gln Gly Ser Val Ala Gly Glu Glu Pro Gly Leu Ser Lys Gln His
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                                                     110
Val Glu Phe Glu Pro Asp Ala Glu Val Leu Thr Asp Gln Arg Arg Pro
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                                                         15
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		-	agc Ser		_	-				-			•			144
			att Ile												·	192
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-	-		gcc Ala 100							-					3	336
_		_	gtt Val	_			_		-		-	_			3	384
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Gly Thr Ser Ala Gly Val His Val Tyr Asn Val Lys Gln Leu Lys Leu
20 25 30

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•	•	-	_									•	act Thr 95		288
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	-	-		_		-		_	-		_		ctt Leu		384
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Ala Pro Asn Thr Asn Asn Leu Val Ile Ala His Ser Asp Gln Gln Val 50 55 60

Phe Glu Tyr Ser Ile Pro Asp Lys Gln Tyr Thr Asp Trp Ser Arg Thr 65 70 75 80

Val Gln Lys Gln Gly Phe His His Leu Trp Leu Gln Arg Asp Thr Pro 85 90 95

Ile Thr His Ile Ser Phe His Pro Lys Arg Pro Met His Ile Leu Leu 100 105 110

His Asp Ala Tyr Met Phe Cys Ile Ile Asp Lys Ser Leu Pro Leu Pro 115 120 125

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gag ctt gag gcc gcg ctg ggg aag aag cac aag ggc ggt gat agc tcc 144 Glu Leu Glu Ala Ala Leu Gly Lys Lys His Lys Gly Gly Asp Ser Ser 35 40 45

agt ggc ccc caa cgc ttg gtt tct ttc cgt ctc atc cgg gat ctg cac

Ser Gly Pro Gln Arg Leu Val Ser Phe Arg Leu Ile Arg Asp Leu His

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55

60

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WO 01/29221

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Ser	G1y 50	Pro	G1n	Arg	Leu	Va1 55	Ser	Phe	Arg	Leu	Ile 60	Arg	Asp	Leu	His	
G1n 65	His	Leu	Arg	Glu	Arg 70	Asp	Ser	Lys	Leu	Tyr 75	Leu	His	Glu	Leu	Leu 80	
Glu	Gly	Ser	Glu	11e 85	Tyr	Leu	Pro	Glu	Va1 90	Val	Lys	Pro	Pro	Arg 95	Asn	
Pro	Glu	Leu	Val 100	Ala	Arg	Leu	Glu	Lys 105	Пe	Lys	Ile	Gln	Leu 110	Ala	Asn	
Glu	Glu	Tyr 115	Lys	Arg	Ile	Thr	Arg 120	Asn	Val	Thr	Cys	Gln 125	Asp	Thr	Arg	
His	Gly 130	Gly	Thr	Leu	Ser	Asp 135	Leu	Gly	Lys	Gln	Va1 140	Arg	Ser	Leu	Lys	
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		•	Thr	165		•			170					175		
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Ala	Arg	Ser	Leu 20	Ser	Arg	Phe	Arg	G1y 25	Cys	Leu	Ala	Gly	Ala 30	Leu	Leu	
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_		_	_	-		gtc Val 55	_	-	-		-	-			_	192
		-				gaa Glu	-	_				-	-		_	240
_	-		-			cag Gln		_		-	_		_		_	288
	-	-				aga Arg						-		-		336
-					_	gga Gly	-	-		-		_	_		-	384
						gtc Val 135										432
						aat Asn		-	Ala							480
	-	-		-	-	gtc Val	-	-			-		-			528
-	_	-	-			gcc Ala			-					-		576
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Leu	Gln	Ala 195	Leu	Ala	Val	His	Leu 200	Ala	Leu	Gln	Gly	G1u 205	Ser	Ser	Ser	
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					ttg Leu 230											720
			-	_	ctg Leu	-	_						-	_	_	768
_					gaa Glu										_	816
_			_	_	ccc Pro		-			_			-	-	_	864
					atc Ile											912
					tca Ser 310				-		-			-		960
	Ala	Gly	Ala	Пe	gct Ala	Gly	Ala	Tyr	Tyr	Gly	Met	Asp	Gln	Val		1008
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384

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Glu	Ser	Trp	G1n 340		Ser	Cys	Glu	G1y 345		Glu	Glu	Thr	Asp 350		Leu	
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Ser		Gly		Ser	Arg		Pro		tgt Cys							192
			-	_				-	atc Ile	-		-		•		240
				-	-		-	_	ctg Leu 90	-		_	-	_		288
cga	ggg	gag	cta	cag	cqa	gtc	сса	acc	ctg	cta	cta	CCC	atq	cct	acq	336

Arg	Gly	Glu	Leu 100	Gln	Arg	Val	Pro	Thr 105	Leu	Leu	Leu	Pro	Met 110	Pro	Thr	
	ccg Pro	-	_			-				_		_		_		384
	cac His 130															432
_	ggc Gly		_	-		-	_	_				-	_	-	-	480
	cgc Arg															528
	ctc Leu	_	_	-		_			-		-					576
	gta Val										_		-	_		624
	gtc Val 210	_					_	-	-	_				_	-	672
	ttc Phe								_	-				-	-	720
	ttt Phe		Asp													768
	cgg Arg						Arg									816
aga i	qcc	tta	сда	act	cta	agc	cta	cct	cta	acc	caq	tta	cct	ata	tcc	864

Gly	Ala	Leu 275	Arg	Ala	Leu	Ser	Leu 280	Pro	Leu	Thr	Gln	Leu 285	Pro	Val	Ser	
	gag Glu 290															912
	tac Tyr				-	-					•		•		-	960
	gtg Val			-		-		-		-		-				1008
	cag Gln	-		_	-		-		-		-	-	-		-	1056
-	ctg Leu	_				_	-	-	-							1104
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Glu	Arg	Thr 35	Ser	Gly	Gly	Pro	G1u 40	Ala	Ala	Asp	Phe	Ser 45	Asp	Gln	Leu
Ser	Leu 50	Gly	Ser	Ser	Arg	Va1 55	Pro	Arg	Cys	Gly	G1n 60	Gly	Thr	Leu	Leu
65			-		70			Ser		75		_			80
His	Cys	Ser	Pro	A1a 85	Arg	Ala	Ser	Leu	Leu 90	Ala	Ser	Gln	Ala	Leu 95	His
Arg	Gly	Glu	Leu 100	Gln	Arg	Val	Pro	Thr 105	Leu	Leu	Leu	Pro	Met 110	Pro	Thr
Glu	Pro	Leu 115	Leu	Pro	Thr	Asp	Trp 120	Pro	Phe	Leu	Pro	Leu 125	Пe	Arg	Leu
Tyr	His 130	Arg	Ala	Ser	Asp	Thr 135	Pro	Ser	Gly	Leu	Ser 140	Pro	Thr	Asp	Thr
145	·				150			Gln	·.	155					160
•	_			165		•		Val	170				•	175	
Arg.	Leu	Met	Cys 180	Val	Phe	Leu	Val	Asp 185	Ser	Glu	Leu	Phe	Arg 190	Glu	Ser
Pro	Val	G1n 195	His	Leu	Val	Ala	A1 a 200	Leu	Leu	Ala	Gln	Leu 205	Cys	Gln	Pro
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Ser 225	Phe	Pro	Asp	Leu	Tyr 230	Ala	Asn	Phe	Leu	Asp 235	His	Phe	Glu	Ala	Val 240
Ser	Phe	Gly	Asp	His 245	Leu	Phe	Gly	Ala	Leu 250	Val	Leu	Leu	Pro	Leu 255	Glr
Arg	Arg	Phe	Ser 260	Val	Thr	Leu	Arg	Leu 265	Ala	Leu	Phe	Gly	G1u 270	His	Va1
Gly	Ala	Leu 275	_	Ala	Leu	Ser	Leu 280	Pro	Leu	Thr	Gln	Leu 285	Pro	Val	Ser
Leu	G1u 290	Cys	Tyr	Thr	Val	Pro 295	Pro	Glu	Asp	Asn	Leu 300	Ala	Leu	Leu	Gln
Leu 305	Tyr	Phe	Arg	Thr	Leu 310	Val	Thr	Gly	Ala	Leu 315	Arg	Pro	Arg	Trp	Cys 320
Pro	Val	Leu	Tyr	Ala 325	Val	Ala	Val	Ala	His 330	Val	Asn	Ser	Phe	11e 335	Phe
Ser	Gln	Asp	Pro 340	Gln	Ser	Ser	Asp	G1u 345	Val	Lys	Ala	Ala	Arg 350	Arg	Ser
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												-	gtg Val 30			96
											_		ctg Leu			144
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	-						_	-					gat Asp		-	240
									_	-			cag G1n		_	288
													gag Glu 110			336

	_			-	aga Arg			_	-		-				_	384
	-	_	_		gat Asp						_					432
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Gly	Phe	G1 <i>y</i> 35	Gly	Val	His	Ser	G1n 40	Glu	Lys	Ala	Lys	Trp 45	Leu	Gly	Gly	
Ala	Val 50		Asp	Tyr	Phe	Met 55	Arg	Asn	Ala	Asp	Leu 60	Glu	Leu	Asp	Glu	
Va1 65	Glu	Asp	Phe	Leu	Gly 70	Glu	Leu	Leu	Thr	Asn 75	Glu	Phe	Asp	Thr	Val 80	
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Phe	His	His	Phe 100		Arg	Gly	Asp	Gly 105		Ala	Leu	Arg	Glu 110		Ala	
Ser	Cys	Ile		Gln	Arg	Lys	Cys		Val	Thr	Ala	Thr		Leu	Lys	

Thr	Ala 130	Arg	Glu	Thr	Asp	G1u 135		Glu	Asp	Asp	Val 140		Ser	Val	Glu	
Glu 145		Glu	Val	Thr	Ala 150			Asp	Gly	Ala 155	Ala		Asp	Gly	Val 160	
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Glu	Asp	Ile	Val 180	Glu	Asp	Gly	Trp	Thr 185	Ile	Val	Arg	Arg	Lys 190	Lys		
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					cac His											96
					999 Gly											144
Ala		Asp		Gly	ggt Gly	Пe	Phe			Arg						192
					cct Pro 70	Pro										240
					cag Gln											288
ttc	ctc	tcc	aag	act	cgg	gtg	gtc	cag	gag	cac	ggc	999	cgg	gcg	gtg	336

Phe	Leu	Ser	Lys 100	Thr	Arg	Val	Val	Gln 105	Glu	His	Gly	Gly	Arg 110	Ala	Val	٠
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Gln	Val	Leu 35		Pro	Gly	Asp	Ile 40		Tyr	Пe	Phe	Thr 45		Thr	Pro	
Ala	Lys 50		Phe	Gly	Gly	Ile 55	Phe	His	Thr	Arg	Tyr 60		Gln	Ile	His	
Leu 65		Prò	Ala	Glu	Pro 70		Glu	Ala	Cys	G1y 75	Glu	Leu	Ser	Asn	Gly 80	
	Phe	Ile	Gln	Asp		Пe	Ala	Leu		_	Arg	Gly	Gly			
				85					90					95		

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Пe	Gln 130	Asp	Ser	Thr	Gln	Arg 135	Thr	Ala	Asp	Пe	Pro 140	Аlа	Leu	Phe	Leu	
Leu 145	Gly	Arg	Asp	Gly	Tyr 150	Met	Ile	Arg	Arg	Ser 155	Leu	G1u	Gln	His	Gly 160	
		·		165			Ile		170			Thr	Ser	I1e 175	Pro	
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							acc Thr			_			_			96
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							gcc Ala									192
							aac Asn							-		240
-							ctg Leu		-	-				-	-	288

		-		-	caa G1n					-		-			_	336
-				_	gat Asp	_	_		_						_	384
				_	gtg Val											432
•	_	_			ata Ile 150	_	-	_	_		-	_	_			480
	-				cag Gln		-				-					528
		-		_	cac His		_				-	_	_	_		576
			-	_	ttt Phe		-		_			_				624
	_	_		_	gcg Ala				_		-		_			672
					gtc Val 230											720
					att Ile											768
		-		_	ggc Gly			-						-		816

			Phe	ctc Leu			Val					864
		Val		gca Ala								912
	Leu			ctc Leu 310								960
				cac His						 _		1008
				ttc Phe								1056
				tcc Ser								1104
				ctc Leu								1152
				cac His 390								1200
			Ala	agt Ser			Cys					1248
		Pro		acg Thr		Пe						1296
cat His	Leu				Val				Leu			1344

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Ile	Ser	Lys	Gly	Ile 245		Glu	Ala	Arg	Phe 250	Val	Tyr	Val	Phe	Va1 255	Leu
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		275					280				Trp	285		-	
	290					295					Pro 300				
Va1 305	Leu	Ala	Phe	Ser	Leu 310	Leu	He	Gln	Thr	Leu 315	Met	Thr	Lys	Phe	I1e 320
				325		•			330		Thr			335	
			340					345			Asn		350		
		355					360				Leu	365		-	
	370					375					Thr 380			_	
385					390					395	Ser				400
				405					410		Tyr			415	-
			420					425			Thr		430	_	
		435					440				Leu	445			•
	450					455		Val	Cys	Val	Phe 460	Phe	Thr	Ala	Met
465	Gin	Inr	Arg	Leu	1hr 470	Gin	Ser								
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	_				_	ccc Pro									_		96
	_		-	_	-	ggc Gly						-	-	-			144
				_	-	cgc Arg 55	_	-	-	_	-	_	_		_		192
						tat Tyr											240
_				-		agc Ser	-										288
	_	_	-			ctc Leu					-						336
			_	-		tgg Trp	-	-			_		_		_		384
_						cag Gln 135		-									432
						cgg Arg											480
ggt	gcc	cgt	gtg	att	gtg	aca	gac	acg	tgg	gtg	atg	aag	gta	acc	acc	,	528

Gly	Ala	Arg	Val	Ile 165	Val	Thr	Asp	Thr	Trp 170	Val	Met	Lys	Val	Thr 175	Thr	
	_			gtg Val	-	-						_		-	_	576
			_	cat His			-		_	_		-			_	624
				cgt Arg		-	-				-		_	_		672
~			_	aac Asn								-	-	-		720
	-			cgc Arg 245		_	-			-			-	-	-	768
	-	_		ctg Leu												816
				ccc Pro												864
_	-		_	gcc Ala	-		-						-			912
				tgc Cys												960
	-	-		aag Lys 325			-	-	-							1008
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400

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		195					200					205				
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Arg	Ala	Pro	Пe	Arg 245	Arg	Ala	Ala	His	Va1 250	Val	Ile	His	Gln	Ser 255	Leu	
Gly	Asp	Leu	Phe 260	Leu	Glu	Xaa	Phe	A1a 265	Ser	Leu	Val	Glu	Va1 270	Asn	Pro	
Ala	Tyr	Ser 275		Pro	Ser	Ser	G1n 280	Glu	Leu	Glu	Ala	Cys 285	Ile	Gly	Cys	
Met	G1n 290	Thr	Arg	Ala	Ser	Va1 295	Lys	Leu	Val	Lys	Thr 300	Cys	Gln	Glu	Ala	
A1a 305	Thr	Gly	G1u	Cys	Gln 310	Gln	Cys	Tyr	Cys	Arg 315	Pro	Met	Trp	Cys	Leu 320	
Thr	Cys	Met	Gly	Lys 325	Trp	Phe	Ala	Ser	Arg 330	G1n	Asp	Pro	Leu	Arg 335	Pro	
Asp	Thr	Trp	Leu 340	Ala	Ser	Arg	Val	Pro 345	Cys	Pro	Thr	Cys	Arg 350	Ala	Arg	
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				_	-	tgc Cys 55					_		-				192
				-		gag G1u							-			;	240
						acg Thr		His								;	288
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				_		tgt Cys				-						;	384
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	-			_	_	gaa G1u	_			-		-		_	-	4	480
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						gcc Ala										į	576
						aac Asn						_		-	_	6	624
-		_				tct Ser 215			_					_	-	6	572

403

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-		-	_		_	_	-				ctc Leu		144
	_	_	_	_							gac Asp		192
											ctg Leu		240
											ctc Leu 95		288
											cca Pro		336

					ctg Leu				_			-				384
					tca Ser											432
			_	_	gag Glu 150	_	_			_	-					480
					aac Asn	_	-	-		_	_		-	_		528
					gtg Val											576
					acc Thr											624
_	_				ctg Leu	-	_				-	_		_		672
		_	_		ggc Gly 230	_	-	_								720
					ctg Leu							-		_		768
					ctg Leu									-	;	816
					ctg Leu											864

		Gln							gac Asp						ctc Leu	912
									gag Glu							960
	-	-				gtg Val			gcc Ala 330	taa *						993
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Met		400> Glu		Δla	G1v	Pro	Δra	l eu	Pro	Leu	Val	ا ھا	lve	Thr	l ou	
1	Alu	uiu	1113	5	uly	110	AI 9	LCu	10	Leu	Vai	Leu	Lys	15	Leu	
Ala	Cys	Thr	His 20	Ser	Ser	Ala	Tyr	G1u 25	Asn	Gln	Arg	Val	Thr 30	Thr	Thr	
Ala	Phe	Leu 35	Ala	Glu	Leu	Leu	Asn 40	Ser	Asn	Val	Ala	Asn 45	Asp	Leu	Met	
Leu	Leu 50	Asp	Ser	Leu	Leu	G1u 55	Ser	Leu	Ala	Ala	Arg 60	Gln	Lys	Asp	Thr	
Cys 65	Ala	Xaa	Val	Arg	Arg 70	Leu	Val	Leu	Arg	G1y 75	Leu	Ala	Asn	Leu	A1 a 80	
Ser	Gly	Cys	Pro	Asp 85	Lys	Val	Arg	Thr	His 90	Gly	Pro	Gln	Leu	Leu 95	Thr	
Ala	Met	Ile	Gly 100	Gly	Leu	Asp	Asp	Gly 105	Asp	Asn	Pro	His	Ser 110		Val	
۵1ء	Leu	Glu		Met	Leu	Gly			Arg	Leu	Val			Val	Glu	
ЛΙЦ		115					120					175				
		115 Asp	Leu	Arg	Ser	Gly 135	120 Leu	Leu	His	Val	Ala 140	125 Ile	Arg	Ile	Arg	

Leu	Phe	Gly	His	Leu 165	Asn	Lys	Val	Cys	His 170	Gly	Asp	Cys	Glu	Asp 175	Val	
Phe	Leu	Asp	Gln 180	۷a٦	Val	Gly	Gly	Leu 185		Pro	Leu	Leu	Leu 190		Leu	
G1n	Asp	Pro 195	Gln	Ala	Thr	Val	Ala 200	Ser	Ala	Cys	Arg	Phe 205	Ala	Leu	Arg	
Met	Cys 210	Gly	Pro	Asn	Leu	Ala 215		Glu	Glu	Leu	Ser 220		Ala	Phe	Gln	
Lys 225	His	Leu	Gln	Glu	Gly 230	Arg	Ala	Leu	His	Phe 235	Gly	Glu	Phe	Leu	Asn 240	
Thr	Thr	Cys	Lys	His 245	Leu	Met	His	His	Phe 250	Pro	Asp	Leu	Leu	Gly 255	Arg	
Leu	Leu	Thr	Thr 260	Cys	Leu	Phe	Tyr	Phe 265	Lys	Ser	Ser	Trp	G1u 270	Asn	<u>V</u> al	
Arg	Ala	A1a 275	Ala	Pro	Leu	Phe	Thr 280	Gly	Phe	Leu	Val	Leu 285	His	Ser	Glu	
Pro	Arg 290	Gln	Gln	Pro	Gln	Va1 295	Asp	Leu	Asp	Gln	Leu 300	Пe	Ala	Ala	Leu	
G1n 305	Ile	Leu	Leu	Lys	Asp 310	Pro	Ala	Pro	Glu	Val 315	Arg	Thr	Arg	Ala	Ala 320	
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_	ttc Phe	_		-						_						240
	gtġ Val		_	-	_				-			-		-	-	288
	atc Ile															336
	ctc Leu				•		•		-					_	•	384
	aaa Lys 130	-						-			_		_			432
-	ggc Gly															480
-	ctg Leu			_			-			-			_		_	528
_	999 Gly	-	_	_	_	_	_	-	-				-			576
	ctt Leu		-						-							624
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WO 01/29221

409

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Tyr	Pro	Pro	Gln	G1u 165	Ala	Asn	Arg	Ser	17e 170	Thr	Ser	Leu	Ser	Val 175	Ala	
-		-						_				-	-	cct Pro	•	576
•					-				_					ccc Pro		624
	_	_			_		_							aag Lys	_	672
	_	_		_	_			-			-		_	gtg Val		720
			-										-	cag Gln 255		768
-		-									-		-	gac Asp		816
-		-			-		_	-					-	gag G1u		864
-	-	-	-		-			_		-	_		_	tta Leu		912
														cat His		960
														aaa Lys 335		1008
gct	gca	cat	gaa	gct	gag	gaa	gaa	tct	gat	aat	att	gca	gaa	gac	ttc	1056

Ald	Ala	His	G1u 340	Αla	Glu	Glu	Glu	Ser 345	Asp	Asn	Пe	Ala	G1u 350	Asp	Phe	
_	gag Glu		_	-	-		_				-	-		•	_	1104
_	aga Arg 370										-					1152
_	gcg Ala												tag *			1194
		210> 211> 212> 213>	397 PRT	o sap	oiens											
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1									10					1 -		
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Gly	Ser Glu	Ser	20	Gly			His	25	Gln			Glu	30	Arg		
Gly	Glu Val	Ser 35	20 Leu	Gly Arg	Asn	Ser Pro	His 40	25 Ser	Gln Ser	Пe	Ala Asn	G1u 45	30 Ile	Arg Gln	Lys	
Gly Ile Asp Ile	Glu	Ser 35 Glu	20 Leu Tyr	Gly Arg Arg	Asn Leu Pro	Ser Pro 55	His 40 Phe	25 Ser Thr	Gln Ser Ile	Ile Asn Gln	Ala Asn 60	Glu 45 Leu	30 Ile Thr	Arg Gln Ile	Lys Asn Ile	
Gly Ile Asp Ile 65	Glu Val 50	Ser 35 Glu Ile	20 Leu Tyr Leu	Gly Arg Arg Leu	Asn Leu Pro 70	Ser Pro 55 Pro	His 40 Phe Gln	25 Ser Thr Phe	Gln Ser Ile Pro	Ile Asn Gln 75	Ala Asn 60 Glu	Glu 45 Leu Lys	30 Ile Thr Pro	Arg Gln Ile Val	Lys Asn Ile 80	
Gly Ile Asp Ile 65 Ser	Glu Val 50 Asn	Ser 35 Glu Ile Tyr	20 Leu Tyr Leu Pro	Gly Arg Arg Leu Pro 85	Asn Leu Pro 70 Ile	Ser Pro 55 Pro Arg	His 40 Phe Gln His	25 Ser Thr Phe His	Gln Ser Ile Pro Leu 90	Ile Asn Gln 75 Met	Ala Asn 60 Glu Asp	Glu 45 Leu Lys	30 Ile Thr Pro Gln	Arg Gln Ile Val Gly 95	Lys Asn Ile 80 Val	
Gly Ile Asp Ile 65 Ser Tyr	Glu Val 50 Asn Val	Ser 35 Glu Ile Tyr	20 Leu Tyr Leu Pro Ser 100	Gly Arg Arg Leu Pro 85 Pro	Asn Leu Pro 70 Ile Leu	Ser Pro 55 Pro Arg Val	His 40 Phe Gln His	25 Ser Thr Phe His Asn 105	Gln Ser Ile Pro Leu 90 Phe	Ile Asn Gln 75 Met Thr	Ala Asn 60 Glu Asp Met	Glu 45 Leu Lys Lys	30 Ile Thr Pro Gln Ser 110	Arg Gln Ile Val Gly 95 Asp	Lys Asn Ile 80 Val	
Gly Ile Asp Ile 65 Ser Tyr Gly	Glu Val 50 Asn Val	Ser 35 Glu Ile Tyr Thr Ile 115	20 Leu Tyr Leu Pro Ser 100 Ile	Gly Arg Arg Leu Pro 85 Pro Gln	Asn Leu Pro 70 Ile Leu Ser	Ser Pro 55 Pro Arg Val Leu	His 40 Phe Gln His Asn Leu 120	25 Ser Thr Phe His Asn 105 Asp	Gln Ser Ile Pro Leu 90 Phe Glu	Ile Asn Gln 75 Met Thr	Ala Asn 60 Glu Asp Met Trp	Glu 45 Leu Lys Lys His	30 Ile Thr Pro Gln Ser 110 Asn	Arg Gln Ile Val Gly 95 Asp	Lys Asn Ile 80 Val Leu Pro	
Gly Ile Asp Ile 65 Ser Tyr Gly Val	Glu Val 50 Asn Val Val Lys Leu	Ser 35 Glu Ile Tyr Thr Ile 115 Ala	20 Leu Tyr Leu Pro Ser 100 Ile Pro	Gly Arg Arg Leu Pro 85 Pro Gln Thr	Asn Leu Pro 70 Ile Leu Ser	Ser Pro 55 Pro Arg Val Leu Thr 135	His 40 Phe Gln His Asn Leu 120 Ala	25 Ser Thr Phe His Asn 105 Asp	Gln Ser Ile Pro Leu 90 Phe Glu Pro	Ile Asn Gln 75 Met Thr Phe	Ala Asn 60 Glu Asp Met Trp Leu 140	Glu 45 Leu Lys Lys His Lys 125 Tyr	30 Ile Thr Pro Gln Ser 110 Asn	Arg Gln Ile Val Gly 95 Asp Pro Asn	Lys Asn Ile 80 Val Leu Pro	

Asp	Thr	Val	Ser 180	Ser	Ser	Thr	Thr	Ser 185	His	Thr	Thr	Ala	Lys 190	Pro	Ala	
Ala	Pro	Ser 195	Phe	Gly	Val	Leu	Ser 200	Asn	Leu	Pro	Leu	Pro 205		Pro	Thr	
Val	Asp 210	Ala	Ser	Пe	Pro	Thr 215	Ser	Gln	Asn	Gly	Phe 220	Gly	Tyr	Lys	Met	
Pro 225	Asp	Va1	Pro	Asp	Ala 230	Phe	Pro	Glu	Leu	Ser 235	Glu	Leu	Ser	Val	Ser 240	
Gln	Leu	Thr	Asp	Met 245	Asn	Glu	Gln	Glu	G1u 250	Val	Leu	Leu	Glu	G1n 255	Phe	
Leu	Thr	Leu	Pro 260	Gln	Leu	Lys	Gln	Ile 265	Ile	Thr	Asp	Lys	Asp 270	Asp	Leu	
Val	Lys	Ser 275	Ile	Glu	Glu	Leu	A1 a 280	Arg	Lys	Asn	Leu	Leu 285	Leu	Glu	Pro	
Ser	Leu 290	Glu	Ala	Lys	Arg	G1n 295	Thr	Val	Leu	Asp	Lys 300	Tyr	Glu	Leu	Leu	
Thr 305	Gln	Met	Lys	Ser	Thr 310	Phe	Glu	Lys	Lys	Met 315	Gln	Arg	Gln	His	G1u 320	
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Ala	Ala	His	G1u 340	Ala	Glu	Glu	Glu	Ser 345	Asp	Asn	Ile	Ala	G1u 350	Asp	Phe	
Leu	Glu	G1y 355	Lys	Met	Glu	Ile	Asp 360	Asp	Phe	Leu	Ser	Ser 365	Phe	Met	Glu	
Lys	Arg 370	Thr	He	Cys	His	Cys 375	Arg	Arg	Ala	Lys	G1u 380	Glu	Lys	Leu	Gln	
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			G1n													70
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Val	Arg	Asn	Ser 20	Lys	Lys	Arg	Pro	A1a 25	Ser	Pro	Ser	His	Asn 30	Gly	Ser	
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						agc Ser 55										192
						aca Thr										240
						aac Asn										288
						aga Arg										336
						ccg Pro			-		-					384
						tcc Ser 135										432
	Ser	Gly	Leu	Leu	Ala	aac Asn	Tyr	Thr	Asp	Pro	Gln			Leu		480
						ttt Phe										528
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tga																579

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									aga Arg	-		_	_	-	192
~		•	-	•	-				 aat Asn 75		_		-		240
									aac Asn						288
	-				-	_			cga Arg	-	-				336
									tct Ser						384
									cta Leu						432
									tca Ser 155						480
				-		_	_		cag Gln				-		528

	_	•			gat Asp			_	_	•			_		576
					ctg Leu										624
		-			gat Asp 215	_	_		_	•	_			-	672
					aag Lys										720
	-		_		cag Gln	-		_	-		_	_	•	•	768
	_		-	_	gaa Glu			•		•					816
_					cat His	-	-		_		_	_			864
					gag G1u 295										912
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<211> 315

<212> PRT

<213> Homo sapiens

<400> 284

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Lys	Gly	Lys 35	Gly	Arg	Asn	Thr	Gly 40	Lys	Ser	Gln	Thr	Leu 45	Gly	Ser	Lys
	50				Lys	55				-	60				
G1n 65	Gln	Gln	Ser	Glu	A1a 70	Asn	Glu	Leu	Arg	Asn 75	Leu	Ala	Phe	Lys	Lys 80
He	Pro	Gln	Lys	Ser 85	Ser	His	Ala	Val	Cys 90	Asn	Ala	Gln	His	Asp 95	Leu
			100		Val			105					110	•	
	·	115		-	Asp		120					125			
·	130		-		Leu	135					140	,			
145		,			Asp 150					155				-	160
		_	-	165	Lys	_			170				·	175	
			180		Lys	•		185			•		190		•
-		195			Val		200	·		_		205			-
	210				Lys	215					220			•	
225			•		A1a 230					235	-		_		240
Gln	Leu	Leu	Lys	Met 245	Leu	Gln	Glu	Gly	G1u 250	Met	Lys	Asp	Lys	A1 a 255	Glu
Ile	Leu	Leu	G1n 260	Val	Asp	Glu	Ser	G1n 265	Ser	Пe	Lys	Asn	G1u 270	Leu	Thr
Ile	Gln	Val 275	Thr	Ser	Leu	His	Ala 280	Ala	Leu	Glu	Gln	G1u 285	Arg	Ser	Lys
Val	Lys 290	Val	Leu	Glņ	Ala	G1u 295	Leu	Ala	Lys	Tyr	G1n 300	Gly	Gly	Arg	Lys
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<211> 1308

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	gac Asp 50		-					-				-	•		-	192
	gcc Ala		-				-		-		-			_		240
	tgg Trp				-	-		-						-	-	288
	ctg Leu			-	_	_		_						-	-	336
	atg Met															384
	ata Ile 130										_					432
ctt	tgg	aag	cat	999	aat	ctg	cga	aat	gtg	ctg	atc	ttg	atg	gat	caa	480

Leu 145		Lys	His	Gly	Asn 150	Leu	Arg	Asn	Val	Leu 155		Leu	Met	Asp	Gln 160	
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					tcc Ser											576
					tct Ser											624
					gaa Glu											672
					gac Asp 230											720
					ttt Phe											768
					gag Glu											816
			Phe		gaa Glu	Glu	Ile	Lys	Lys	-	Leu					864
					ccc Pro											912
				Cys	att Ile 310											960
gta	tta	gac	cgt	ctc	ctt	gat	cag	gat	cta	cca	agg	gcc	agg	gat	ttc	1008

Val	Leu	Asp	Arg	Leu 325	Leu	Asp	Gln	Asp	Leu 330	Pro	Arg	Ala	Arg	Asp 335	Phe		
	agg Arg			_								-	-		-	10	56
	atc Ile											-				110)4
	atc Ile 370		-	-	-	-				_	_	-	-			11!	52
_	acc Thr	•							-	-	•		_			120)0
•	ctc Leu		-		-		-	_	_		-	-	_	•	_	124	18
	gag Glu		-	_					-	-	-				_	129) 6
	cct Pro	_	taa *													130)8
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Trp	Ser	His 35	20 Arg	Arg	His			25 Gln	Gln	Gly	Glu	G1n 45	30 Gln	Gln	Ile		

Pro	Asp 50	Pro	Cys	Arg	Leu	Ser 55	Thr	Ala	Thr	Leu	Lys 60	Cys	Leu	Gln	Ala
G1n 65	Ala	Met	Arg	Glu	Gly 70	Leu	Ala	Lys	Glu	Ser 75	Asp	Glu	Gly	Asp	Asn 80
Leu	Trp	Thr	Leu	Leu 85	Ser	Ser	Pro	Ser	Thr 90	His	His	Пe	Gly	Va1 95	Cys
Ser	Leu	Αla	Arg 100	Ser	Met	Ala	Val	Trp 105	Gln	His	Gly	Val	Ile 110	Leu	Asp
Ile	Met	Glu 115	Gln	Leu	Leu	Ser	Ser 120	Leu	Thr	Ser	Ser	Ser 125	Glu	Asn	Tyr
Arg	Ile 130	Thr	Gly	Ala	Ala	Phe 135	Phe	Ser	Glu	Leu	Met 140	Lys	Glu	Pro	He
Leu 145	Trp	Lys	His	Gly	Asn 150	Leu	Arg	Asn	Val	Leu 155	Пe	Leu	Met	Asp	Gln 160
Ser	Ala	Trp	Asp	Ser 165	Asn	Ala	Thr	Leu	Arg 170	Gln	Met	Ala	Ile	Arg 175	Gly
Leu	Gly	Asn	Thr 180	Ala	Ser	Gly	Ala	Pro 185	His	Lys	Val	Lys	Lys 190	His	Lys
G1n	Leu	Met 195	Leu	Glu	Ser	He	Ile 200	Arg	Gly	Leu	Tyr	His 205	Leu	Ala	Arg
Thr	Glu 210	Val	Val	Cys	Glu	Ser 215	Leu	Lys	Ala	Leu	Lys 220	Lys	Ile	Leu	Glu
Leu 225	Leu	Thr	Asp	Arg	Asp 230	Val	Ser	Phe	Tyr	Phe 235	Lys	Glu	Ile	Val	Leu 240
Gln	Thr	Arg	Thr	Phe 245	Phe	Glu	Asp	G1u	G1n 250	Asp	Asp	Val	Arg	Leu 255	Thr
Ala	Ile	Phe	Leu 260	Phe	Glu	Asp	Leu	A1a 265	Pro	Leu	Thr	Gly	Arg 270	Arg	Trp
Lys	Ile	Phe 275	Phe	Ala	Glu	Glu	Ile 280	Lys	Lys	Ser	Leu	I1e 285	Ser	Phe	Leu
Leu	His 290	Leu	Trp	Asp	Pro	Asn 295	Pro	Lys	Ile	Gly	Val 300	Ala	Cys	Arg	Asp
Va1 305	Leu	Met	Val	Cys	Ile 310	Pro	Phe	Leu	Gly	Leu 315	Gln	Glu	Leu	Tyr	G1y 320
Val	Leu	Asp	Arg	Leu 325	Leu	Asp	Gln	Asp	Leu 330	Pro	Arg	Ala	Arg	Asp 335	Phe
Tyr	Arg	Gln	Phe 340	Cys	Val	Lys	Leu	A1a 345	Lys	Lys	Asn	Gln	G1u 350	Пe	Leu
Trp	Пe	Leu 355	His	Thr	His	Ser	Phe 360	Thr	Phe	Phe	Thr	Ser 365	Thr	Trp	Glu
Val	Ile 370		Ser	Ala	Ala	Va1 375		Leu	Thr	Asp	Ala 380	Val	Val	Leu	Asn
Leu 385		Ser	Gln	Tyr	Va1 390	Glu	Leu	Leu	Asp	Arg 395	Glu	Gln	Leu	Thr	Thr 400

Ala		Ala	Ala Ala 420	405	Ť		•		410					415		
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			aac Asn													240
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			tcc Ser 100				-	_	_							336

					gtg Val										384
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					cag Gln				_	_	_	-	-	-	528
	-	_	 		ctg Leu							-			576
					agg Arg						_	-		-	624
					atg Met 215										672
-			 -	-	tgc Cys	-		-	-			-			720
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PCT/US00/29052

WO 01/29221

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Phe	Ser	Gly		Glu	Ser	Ala	Leu		Ser	Leu	Lys	Asn		Gln	Ala	
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Cys	He		Ser	Gly	Met	Asp		Ala	Ser	Ser	Val		Leu	Asp	Leu	
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Val		Ser	Gln	Thr	Glu	Val	Ser	Ser	Glu	Tyr		Met	Asp	Lys	Ala	
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	Val	Glu	Phe	Ala		Leu	Asp	Arg	Gln		Asn	His	Tyr	Val	•	
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41 a	Val	Gln	Ser		Пe	Asn	His	Val		Glu	Glu	Arg	Pro		Lys	
				85					90					95		
		_				ttg	-		-			_	•		•	336
He	Pro	Asp		Lys	Leu	Leu	Val		Lys	Lys	Phe	Leu		Leu	Gln	
			100					105					110			
agc	aag	aat	tct	gat	gca	gac	ttt	caa	aat	aat	gaa	aaa	ttt	gta	cag	384
Ser	Lys		Ser	Asp	Ala	Asp		Gln	Asn	Asn	Glu		Phe	Val	Gln	
		115					120					125				
tt	aaa	caa	caq	ctq	aaa	gaa	cta	aaq	aaq	caa	tat	qat	ctt	caa	act	432

Phe	Lys 130	Gln	Gln	Leu	Lys	G1u 135	Leu	Lys	Lys	G1n	Cys 140	Gly	Leu	Gln	Ala		
				-			gaa Glu				_	_				4	480
		-	-				acc Thr					_		-	•	,	528
_	-						gtg Val	_					-		_	į	576
							tcc Ser 200			_		_		-	_	· (524
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1				5					10					15			
			20					25					30				
ys		Asn 35	Ser	Gly	Met		Thr 40	Ala	Ser	Ser	Val	A1a 45	Leu	Asp	Leu		

Val	Glu 50	Ser	Gln	Thr	Glu	Va1 55	Ser	Ser	Glu	Tyr	Ser 60	Met	Asp	Lys	Ala	
Met 65	Val	Glu	Phe	Ala	Thr 70	Leu	Asp	Arg	Gln	Leu 75	Asn	His	Tyr	Val	Lys 80	
Ala	Val	Gln	Ser	Thr 85	He	Asn	His	Val	Lys 90	Glu	Glu	Arg	Pro	G1u 95	Lys	
Ile	Pro	Asp	Leu 100	Lys	Leu	Leu	Val	Glu 105	Lys	Lys	Phe	Leu	Ala 110	Leu	Gln	
Ser	Lys	Asn 115	Ser	Asp	Ala	Asp	Phe 120	Gln	Asn	Asn	Glu	Lys 125	Phe	۷a۱	Gln	
Phe	Lys 130	G1n	Gln	Leu	Lys	Glu 135	Leu	Lys	Lys	Gln	Cys 140	Gly	Leu	Gln	Ala	
Asp 145	Arg	Glu	Ala	Asp	Gly 150	Thr	Glu	Gly	Val	Asp 155	G1u	Asp	Пe	Пe	Val 160	
Thr	Gln	Ser	Gln	Thr 165	Asn	Phe	Thr	Cys	Pro 170	Ile	Thr	Lys	Glu	Glu 175	Met	
Lys	Lys	Pro	Val 180	Lys	Asn	Lys	Val	Cys 185	Gly	His	Thr	Tyr	G1u 190	Glu	Asp	
Ala	Ile	Val 195	Arg	Met	Ile	Glu	Ser 200	Arg	Gln	Lys	Arg	Lys 205	Lys	Lys	Ala	
Tyr	Cys 210	Pro	Gln	He	Gly	Cys 215	Ser	His	Thr	Asp	Ile 220	Arg	Lys	Ser	Asp	
Leu 225	Ile	Gln	Asp	Glu	A1a 230	Leu	Arg	Arg	Ala	Ile 235	Glu	Asn	His	Asn	Lys 240	
Lys	Arg	His	Arg	His 245	Ser	Glu										
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1	Ala	uiu	1112	5	aly	-10	AI Y	Leu	10	Leu	vai	LEU	Lys	15	Leu	

										_		-		acc Thr	90
_		_	-		-	-					-		-	atg Met	144
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			gtg Val											gcc Ala 80	24(
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	_		ggc Gly 100			_	_		_				-		336
			gcc Ala					-		_	_		-	 	384
			ctg Leu								-		_		432
			gac Asp	-								-		cgc Arg 160	480
			cac His												528
		Asp	cag Gln 180												576

				acc Thr											624
 -				ctg Leu	-	-					-	•		•	672
		-		ggc Gly 230	_	-									720
	_	_		ctg Leu	_					-	-	_		-	768
-			_	ctg Leu				_	-	_				-	816
				ctg Leu											864
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				gga gtg gat Gly Val Asp		240
				ttg aat act Leu Asn Thr		288
		Ala Ala A		agc tta acc Ser Leu Thr 110		336
ctt aag aag Leu Lys Lys 115						384
ggg gac acg Gly Asp Thr 130			er Ile Arg			432

					acc Thr 150												480
				-	agg Arg				_								528
_		_	_		ttt Phe								_		-		576
	_				gcc Ala	_	-			_		_	-	_	_		624
_	-		_		gaa Glu			_			-		_	-			672
	_			-	gaa Glu 230	_				-	_			-			720
_					agt Ser	_	_		-		-			-	-	,	768
-				_	gca Ala			-			-		-				816
_	_	_	-		gga Gly		-		_			-			_		864
				-	acc Thr		_	_		_			_				912
				_	cag Gln 310	-	_	_					-		_		960

434

					cac His								1008
_			-	-	gct Ala		_	_	-		•		1056
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Val	Tyr	Asp	Gln 180	Pro	Phe	His	Ser	Ser 185	Ala	Leu	Glu	Lys	Glu 190	Glu	Ala	
Leu	Ser	Asn 195	Pro	Gly	Ala	Leu	Asp 200	Leu	Pro	Ser	Leu	Thr 205	Ser	Leu	Leu	
Ser	Glu 210	Lys	Ala	Lys	Glu	Phe 215	Leu	Met	Glu	Asn	Arg 220	Val	Gln	Ser	Phe	
Tyr 225	Gln	Gln	Glu	Leu	G1u 230	Met	Val	Glu	Ser	Leu 235	Leu	Ser	Leu	Ala	Asn 240	
Gln	Pro	Val	He	His 245	Ser	Ala	Cys	Ser	Asp 250	Gln	Val	Asn	Phe	Lys 255	Lys	
Asp	Thr	Thr	Ser 260	Lys	Ala	Пe	His	Ser 265	Пe	Phe	Lys	Asn	Ala 270	He	Gln	
Leu	Leu	G1n 275	Glu	Lys	Gly	Leu	Val 280	Phe	Gln	Lys	Asp	Asp 285	Gly	Phe	Asp	
Asn	Leu 290	Tyr	Tyr	Val	Thr	Arg 295	Glu	Asp	Lys	Asp	Leu 300	His	Arg	Lys	Ile	
His 305	Arg	Ile	Пе	Gln	G1n 310	Asp	Cys	Gln	Lys	Pro 315	Asn	His	Met	Glu	Lys 320	
Gly	Cys	His	Phe	Leu 325	His	He	Leu	Ala	Cys 330	Ala	Arg	Leu	Ser	Ile 335	Arg	
Pro	Gly	Leu	Ser 340	Glu	Ala	Val	Leu	G1n 345	Gln	Val	Leu	Glu	Leu 350	Leu	Glu	
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			ggc Gly							-		240
			gca Ala									288
			gaa Glu					-	-	-	;	336
			aat Asn								;	384
			aac Asn 135								4	432
			cta Leu								2	480
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437

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<400> 296

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His Arg Arg Ser His Gln His Met Ser Pro Leu Ala Ala Gln Glu Met 35 40 45

Ser Val Arg Met Ser Asn Leu Glu Asn Asp Arg Asp Glu Arg Asp Asp 50 55 60

Asp Ser His Glu Asp Arg Gly Ile Ile Ser Asn Thr Arg Phe Ile Ala 65 70 75 80

Ala Val Ile Glu Arg His Ala His Ser Pro Glu Arg Arg Arg Tyr 85 90 95

Trp Gly Arg Ser Gly Thr Glu Ser Asp His Gly Tyr Ser Thr Met Ser 100 105 110

Pro Gln Glu Asp Ser Glu Asn Pro Pro Cys Asn Asn Asp Pro Leu Ser 115 120 125

Ala Gly Val Asp Val Gly Asn His Asp Glu Asp Leu Asp Leu Asp Thr 130 135 140

Pro Pro Gln Thr Ala Ala Leu Leu Ser His Lys Phe His His Tyr Arg 145 150 155 160

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Thr Val His Thr Val Asp Ala Glu Cys 180 185

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1 5 10 15

96

gtc agc aac gat ccc gat gtc atc aag ttg caa gag att cca acc ttc Val Ser Asn Asp Pro Asp Val Ile Lys Leu Gln Glu Ile Pro Thr Phe

438

			20					25					30			
-			-				_	_		_	act Thr					144
-		-			-	_		-	-		ttg Leu 60	_		_		192
-			_		_						gcc Ala	-	-		-	240
											gat Asp					288
	_		_		_	_		-	_		aga Arg		-	_		336
-		-		-					_		gcc Ala			-	-	384
	_	-			-	-				_	ctg Leu 140	- ,				432
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<211> 166

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			- 20					25					30				
						tta Leu											144
-			_	-		gct Ala 55		-		_	-	-	_	-	_	1	192
	-	-	-	_		gga Gly	_	-		_	-	_	-			Ź	240
	-		_			aca Thr				_				_	-	2	288
	_			_		ctt Leu	_				_	_	-		_	3	336
			-	_		tca Ser									-	3	384
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			_		-	ttt Phe				-	-	-			_	5	528
						gat Asp										5	576
				_	-	atg Met		-	_		-			-	-	6	524

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	tat Tyr		-						•							828
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ys	Leu	Pro 35	Gly	Leu	He		Phe 40	Met	Asp	His	Pro	Asn 45	Pro	Pro	Val	
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Asn	Val	He	Gln	Lys 85	Thr	Thr	Thr	Pro	G1 <i>y</i> 90	Glu	Thr	Lys	Leu	Leu 95	Ala		
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Leu 145		Asp	Thr	Ser	Arg 150	Arg	Asn	Leu	Cys	G1u 155	Glu	Ala	Leu	Leu	Ly <u>s</u> 160		
Пe	Lys	Gly	Val	Ile 165	Ser	Phe	Thr	Phe	G1n 170	Met	Ala	Val	Gln	Arg 175	Cys		
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Thr	Lys	Glu	Gln	Asp 245	Lys	Ala	Val	Ser	Arg 250	Val	Gly	Ser	His	Pro 255	Glu		
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Gln Gln Gln Ser Glu Ala Asn Glu Leu Arg Asn Leu Ala Phe Lys Lys
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Ile Pro Gln Lys Ser Ser His Ala Val Cys Asn Ala Gln His Asp Leu
Pro Leu Ser Asn Pro Val Gln Lys Asp Ser Arg Glu Glu Asn Trp Gln
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                                105
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Glu Trp Arg Gln Arg Asp Glu Gln Leu Thr Ser Glu Met Phe Glu Ala
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                            120
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Asp Leu Glu Lys Ala Leu Leu Leu Ser Lys Leu Glu Tyr Glu Glu His
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Lys Lys Glu Tyr Glu Asp Ala Glu Asn Thr Ser Thr Gln Ser Lys Val
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Met Asn Xaa Lys Asp Lys Arg Lys Asn His Gln Gly Lys Asp Arg Pro
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                                    170
Leu Thr Val Ser Leu Lys Asp Phe His Ser Glu Asp His Ile Ser Lys
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Lys Thr Glu Glu Leu Ser Ser Ser Gln Thr Leu Ser His Asp Gly Gly
Phe Phe Asn Arg Leu Glu Asp Asp Val His Lys Ile Leu Ile Arg Glu
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Lys Arg Arg Glu Gln Leu Thr Glu Tyr Asn Gly Thr Asp Asn Cys Thr
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Ala His Glu His Asn Gln Glu Val Val Leu Lys Asp Gly Arg Ile Glu
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Arg	Asn 290	Ala	Gln	Leu	Leu	Lys 295	Met	Leu	Gln	Glu	Gly 300	Glu	Met	Lys	Asp	
Lys 305	Ala	Glu	Ile	Leu	Leu 310	Gln	Val	Asp	Glu	Ser 315	Gln	Ser	Ile	Lys	Asn 320	
Glu	Leu	Thr	Ile	G1n 325	Val	Thr	Ser	Leu	His 330	Ala	Ala	Leu	Glu	G1n 335	Glu	
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-			gct Ala				-					_		-		240

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-				-	-		act Thr									288
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				-			agc Ser 120			_						384
-	-						tgt Cys	_	-	-	-	_	_			432
-				_	-		gca Ala	-					_		agg Arg 160	480
	-		_				cct Pro	_			-		-	_		528
					-	_	gaa G1u			-		_				576
							ctg Leu 200									624
-			-				gat Asp	_	-					-	-	672
_			-	-	_		gcc Ala	-			_			-	-	720
	-		-				aag Lys			-			-			768

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235

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225

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						atg Met 55			-	-						192
						gcc Ala										240
						cag Gln	-		-				-		-	288
						ttt Phe				•		-			_	336
						atg Met		-						-	_	384

450

	115			120				125				
							atc Ile 140					432
							atc Ile		_			480
						_	ttg Leu			_		528
							cct Pro				-	576
							ctg Leu				_	624
							ttg Leu 220					672
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	-			-	-		cct Pro	-	_	-		768
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				act Thr	_	_		_	-		-	336
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				att Ile 135		_				-		432
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•	ata Ile 210		_										-			672
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-	tac Tyr	-					-				_			_		768
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Lys	Thr	A1a 35		Leu	Asp	Tyr	Ile 40		Arg	Cys	Arg	Pro 45		Asp	Ser	
Glu	Lys		Asn	Met	Ile	Ala	Leu	Cys	Phe	Ser	Met	Cys	Arg	`G1u	Пe	

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Leu	Leu	Leu	Lys 100	Ala	Leu	Thr	Leu	Met 105	Leu	Asp	Ala	Ala	Glu 110	Ser	Tyr	
Ala	Lys	Asp 115	Ser	Cys	Val	Arg	Gln 120	Ala	Gln	His	Cys	G1n 125	Arg	Leu	Thr	
Lys	Leu 130		Thr	Leu	Gln	Ile 135	His	Phe	Leu	Asn	Thr 140	Gly	Gln	Asn	Thr	
Met 145	Leu	He	Asn	Leu	Gly 150	Arg	His	Lys	Leu	Met 155	Asp	Cys	Ile	Leu	Ala 160	
Leu	Pro	Arg	Phe	Tyr 165	Gln	Ala	Ser	He	Val 170	Ala	Glu	ΑΊa	Tyr	Asp 175	Phe	
Val	Pro	Asp	Trp 180	Ala	Glu	Ile	Leu	Tyr 185	Gln	Gln	Val	Ile	Leu 190	Lys	Gly	
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	aca Thr														aaa Lys	96
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	ctt Leu				_	_	-	-		_	_	_	-	_	~	144
	aaa Lys 50															192
-	gag Glu	_	-	-		-	-			-						240
-	aaa Lys		_		_	_			_	_		-	_		-	288
_	gaa Glu		-				-		_				-	_	-	336
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Gln	Leu	Tyr 35		Ser	Leu	Met	A1 a 40		His	Ala	Ser	Arg 45		Arg	Val	
Пе	Lys 50		Cys	Пe	Ala	G1n 55		Ser	Ala	Val	Va1 60		Asn	Leu	Arg	
Glu	Glu	Arg	Glu	Lys	Asn		Asp	Asp	Leu	Thr		Leu	Lys	Gln	Leu	

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						ggt Gly 55										192
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		-				gag Glu					-			-		336

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												cct Pro				2	1 32
	_	-	-						_			gca Ala		-	_	2	180
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Met	Gln	Arg 35		Ser	Leu	Arg	Phe 40		Gly	Pro	Met	Thr 45		Ser	Tyr		
Arg	Ser 50		Ala	Arg	Thr	G1y 55	. •	Pro	Arg	Lys	Thr 60	Arg	IJе	Пе	Leu		
G1u 65	-	Glu	Asn	Asp	Ala 70		Ala	Asp	Ala	Asp 75		Leu	Ala	Gly	Pro 80		
	Ala	Ala		Leu 85		Ala	Ala	Thr	Va1 90		Thr	Gly	Phe	Ser 95			
Ser	Ser	Ala			Glu	Glu	Asp	Gly 105		Ser	Glu	Glu	Gly 110		Val		
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Pro 145		Ser	Trp	Gly	Ala 150	Glu	Pro	Ala	Pro	His 155	Gly	Ala	Gln	Ala	Leu 160	
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Gly	His	Lys	Ser 180	Leu	Tyr											
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								ctg Leu 25					-			96
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                                                          15
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                                                                       96
Pro Leu Trp Ser Ser Ser Leu Pro Gly Leu Asp Thr Ala Glu Ser Lys
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gcc acc att gca gac ctg atc ctg tct gcg ctg gag aga gcc acc gtc
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Ala Thr Ile Ala Asp Leu Ile Leu Ser Ala Leu Glu Arg Ala Thr Val
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cta Leu 50											192
cga Arg											240
gag Glu											288
aag Lys		-		_	_				•	_	336
gat Asp								_			384
tgg Trp 130											432
ccc Pro								-		-	480
tgc Cys											528
ggc Gly			-		_	_	-			-	576
ggc Gly	-				_				_	-	624
agg Arg 210		Gln									672

									gag Glu		720
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									tgg Trp		816
									999 Gly		864
	-	-				-			cag G1n	-	912
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Ala	Thr	I1e 35	Ala	Asp	Leu	Пe	Leu 40	Ser	Ala	Leu	Glu	Arg 45	Ala	Thr	Val
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65					G1u 70					75			_		80
				85	Gln				90			•		95	
			100		Ala			105					110		
	·	115	•	•	Leu		120					125			
	130	_			His	135	·				140				
145					Pro 150					155			Ī		160
				165	Leu		-		170		,			175	
	-		180	·	Leu	•	_	185				-	190	-	-
	_	195	-		Ser		200					205	•		
	210	Ť	-		Gln	215					220		•	•	
225					Asn 230			·		235	·				240
	-			245	Pro		_		250					255	
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His 305	Phe	Ser	Arg	Arg	Val 310	Lys	Arg	Arg	Glu	Lys 315	Gln	Phe	Pro	Asp	G1y 320
Cys	Ser	Ser	His	Asn 325	Thr	Ala	Thr	Ala	Va1 330	Ala	Ala	Leu	Gly	G1y 335	Phe
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				-		ttc Phe						_			_	480
-						cgc Arg		-	-				-			528
	_	_	_	-		ctg Leu			_							576
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		-	-			ggc Gly 215								-	-	672
_	-		-			ctg Leu		-				-	-		-	720
						ctg Leu								_	_	768
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-		_			_	ttc Phe		_					-			864

						cag G1n 295									912
_	-		_		_	ttc Phe			-			_	_	~ ~	960
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						gcc Ala									1056
	-		-	-	_	gaa Glu	_	_			-	_	_		1104
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						ctg Leu									1200
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		-	-			atc Ile 455	 	_	_	-	_	_	_		1392

gcc agc ctt ttc ggc ctc tac ttc cac cag cac ttg gca ggc tcc tag 1440 Ala Ser Leu Phe Gly Leu Tyr Phe His Gln His Leu Ala Gly Ser * 465 470 475 <210> 318 <211> 479 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(479) <223> Xaa = Any Amino Acid <400> 318 Met Ala Val Leu Gly Val Gln Leu Val Val Thr Leu Leu Thr Ala Thr Leu Met His Arg Leu Ala Pro His Cys Ser Phe Ala Arg Trp Leu Leu 25 Cys Asn Gly Ser Leu Phe Arg Tyr Lys His Pro Ser Glu Glu Glu Leu 40 Arg Ala Leu Ala Gly Lys Pro Arg Pro Arg Gly Arg Lys Glu Arg Trp 55 Ala Asn Gly Leu Ser Glu Glu Lys Pro Leu Ser Val Pro Arg Asp Ala Pro Phe Gln Leu Glu Thr Cys Pro Leu Thr Thr Val Asp Ala Leu Val 90 Leu Arg Phe Phe Leu Glu Tyr Gln Trp Phe Val Asp Phe Ala Val Tyr 105 Ser Gly Gly Val Tyr Leu Phe Thr Glu Ala Tyr Tyr Tyr Met Leu Gly 120 125 Pro Ala Lys Glu Thr Asn Ile Ala Val Phe Trp Cys Leu Leu Thr Val 130 135 140 Thr Phe Ser Ile Lys Met Phe Leu Thr Val Thr Arg Leu Tyr Phe Ser 150 155 Ala Glu Glu Gly Glu Arg Ser Val Cys Leu Thr Phe Ala Phe Leu 165 170 Phe Leu Leu Ala Met Leu Val Gln Val Val Arg Glu Glu Thr Leu

185

Glu Leu Gly Leu Glu Pro Gly Leu Ala Ser Met Thr Gln Asn Leu Glu 200

Pro Leu Leu Lys Lys Gln Gly Trp Asp Trp Ala Leu Pro Val Ala Lys

190

205

<400> 319

467

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	-		ttc Phe									_		_	_	144
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	_		aaa Lys	_				-	_		-	_		-	-	240
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			gag Glu 100											tga *		333
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			20 Phe					25					30			
		35					40					45				
a i y	50	uıu	Arg	rile	Leu	55	GIU	261.	vdI	rne	5er 60	ı yı.	uin	۷dI	AId	

60

Ser Thr Leu Lys Gln Val Lys His Asp Gln Gln Val Ala Arg Met Glu

65 L v c	Lou	۸1 م	Clu	Lou	70 Val	Clu	Clu	Lou	C1	75	۸	C1	т	۸	80	
				85					90		·		•	95	Phe	
Lys	Pro	He	Glu 100	Gln	Leu	Leu	Gly	Phe 105		Pro	Ser	Ser	Gly 110			
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				gtg Val				_			_	_				192
				cta Leu												240
				tat Tyr 85												288

					aca Thr									336
					gta Val		_				_		_	 384
					cct Pro 135									432
					ggt Gly									480
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	_				cca Pro	_			_	-	-	_		576
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	-	-			gga Gly	-				-		~	•	720
					atg Met									768
-		Leu		-	gct Ala	Thr					-		_	816

													gca Ala		864
													cag Gln		912
													tta Leu		960
											_	_	aga Arg 335		1008
													ctc Leu		1056
	-	-	_		_				-				ccg Pro	_	1104
													gtc Val		1152
									-	_	-	_	ctg Leu	_	1200
				_	_	-	Thr	-	-			-	tgg Trp 415		1248
	Пe					Lys							tcc Ser		1296
Leu					Leu								gag G1u		1344

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Phe Gln Gly Arg Leu Asn Glu Val Ile Arg Thr Leu Thr Gln Val Ile
Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
                        55
Gly His Leu His Leu Ser Thr Leu Ser Ser Ser Gln Ser Arg Ala Ser
                                        75
Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
                                105
Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
                            120
                                                125
Glu Ser Tyr Gln Tyr Pro Pro Val Asn Trp Ala Ala Leu Leu Ser Pro
                        135
                                            140
Leu Met Arg Leu Asn Phe Gly Glu Glu Ile Gln Gln Leu Cys Leu Glu
                    150
Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Leu Leu
                165
                                    170
Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
                                185
                                                    190
Lys Arg Tyr Leu Leu Ile Ser Ala Pro Leu Trp Ile Lys His Ile Ser
                            200
                                                205
Asp Glu Gln Ile Leu Gly Phe Val Glu Asn Leu Met Val Ala Val Phe
   210
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Lys Ala Ala Ser Pro Leu Gly Ser Pro Glu Leu Cys Pro Ser Ala Leu 225 230 235 His Gly Leu Ser Gln Ala Met Lys Leu Pro Ser Pro Ala His His Leu 245 250 Trp Ser Leu Leu Ser Glu Ala Thr Gly Lys Ile Phe Asp Leu Leu Pro 265 Asn Lys Ile Arg Arg Lys Asp Leu Glu Leu Tyr Ile Ser Ile Ala Lys 275 280 285 Cys Leu Leu Glu Met Thr Asp Asp Asp Ala Asn Arg Ile Ala Gln Val 295 300 Thr Lys Ser Asn Ile Glu Lys Ala Ala Phe Val Lys Leu Tyr Leu Val 310 315 Ser Gln Gly Arg Phe Pro Leu Val Asn Leu Thr Asp Met Leu Arg Phe 325 330 Ala Thr Ala Val Val Ala Trp Ala Asp His Thr Ala Pro Leu Leu Leu 340 345 Gly Leu Ser Ala Ser Trp Leu Pro Trp His Gln Glu Asn Gly Pro Ala 360 Gly Pro Val Pro Ser Phe Leu Gly Arg Ser Pro Met His Arg Val Thr 375 380 Leu Gln Glu Val Leu Thr Leu Leu Pro Asn Ser Met Ala Leu Leu Leu 390 395 Gin Lys Glu Pro Trp Lys Glu Gin Thr Gin Lys Phe Ile Asp Trp Leu 405 410 415 Phe Ser Ile Met Glu Ser Pro Lys Glu Ala Leu Ser Ala Gln Ser Arg 425 Asp Leu Leu Lys Ala Thr Leu Leu Ser Leu Arg Val Leu Pro Glu Phe 440 445 . Lys Lys Lys Ala Val Trp Thr Arg Ala Tyr Gly Trp 450 455 460 <210> 323 <211> 1596 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1596) <221> misc feature <222> (1)...(1596)

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-	•							-			-	-		ctt Leu		192
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-			-		-		_		-	_	-			gga Gly 95	_	288
-													-	tct Ser		336
						-		-				-		gtt Val		384
	-									-	-			tct Ser		432
	-						_			_		_	_	ctt Leu	_	480
									_					cta Leu 175		528

					cca Pro											576
					ata Ile											624
-	_	_		-	ggt Gly		-	-			_		•	_		672
	-				ctt Leu 230						-		-	-		720
					gcc Ala											768
	_	_			gaa Glu	_						-		_		816
					aag Lys	-			-			_		-		864
-			-	-	aca Thr	-	-	-	-				-	_	•	912
	_	-			gaa Glu 310		-	_		_		_			•	960
			_		ccc Pro	_			-		-	_		-	-	1008
_		Gln		-	gag Glu		Glu		-	-		-		_		1056

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														aat Asn			1152
-		-								-		-		gct Ala	_		1200
-			_	_					-		-	_		gct Ala 415	-		1248
											_		_	cca Pro			1296
	-				_	_			-		-			ggc Gly			1344
-		-			_		-	_		-				ctt Leu			1392
	_	_	_	-	_		-					-	-	cag Gln			1440
														aaa Lys 495			1488
														ctg Leu			1536
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PCT/US00/29052

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Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
Gly His Leu His Leu Ser Thr Leu Ser Ser Ser Gln Ser Arg Ala Ser
                    70
Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
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Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
                            120
Glu Ser Tyr Gln Tyr Pro Pro Val Asn Trp Ala Ala Leu Leu Ser Pro
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                        135
Leu Met Arg Leu Asn Phe Gly Glu Glu Ile Gln Gln Leu Cys Leu Glu
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                    150
Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Ala Leu Leu
                                    170
Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
                                185
                                                    190
Lys Arg Tyr Leu Leu Ile Ser Ala Pro Leu Trp Ile Lys His Ile Ser
                            200
Asp Glu Gln Ile Leu Gly Phe Val Glu Asn Leu Met Val Ala Val Phe
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Trp	Ser	Leu	Leu 260	Ser	Glu	Ala	Thr	G1y 265	Lys	Ile	Phe	Asp	Leu 270		Pro
Asn	Lys	Ile 275	Arg	Arg	Lys	Asp	Leu 280		Leu	Tyr	Ile	Ser 285	Пe	Ala	Lys
Суs	Leu 290	Leu	Glu	Met	Thr	Asp 295	Asp	Asp	Ala	Asn	Arg 300	Ile	Ala	Gln	Va1
Thr 305	Lys	Ser	Asn	Ile	Glu 310	Lys	Ala	Ala	Phe	Val 315	Lys	Leu	Tyr	Leu	Val 320
Ser	Gln	Gly	Arg	Phe 325	Pro	Leu	Val	Asn	Leu 330	Thr	Asp	Met	Leu	Ser 335	Val
Ala	Val	Gln	His 340	Arg	Glu	Lys	Glu	Va1 345	Leu	Ala	Trp	Met	11e 350	Leu	His
Ser	Leu	Tyr 355	Gln	Ala	Arg	Пe	Val 360	Ser	His	Ala	Asn	Thr 365	Gly	Val	Leu
Lys	Arg 370	Met	Glu	Trp	Leu	Leu 375	Glu	Leu	Met	Gly	Tyr 380	Ile	Arg	Asn	Val
A1a 385	Tyr	Gln	Ser	Thr	Ser 390	Phe	His	Asn	Thr	A1a 395	Leu	Asp	Glu	Ala	Leu 400
Asp	Phe	Phe	Leu	Leu 405	He	Phe	Ala	Thr	Ala 410	Val	Val	Ala	Trp	A1a 415	Asp
His	Thr	Ala	Pro 420	Leu	Leu	Leu	Gly	Leu 425	Ser	Ala	Ser	Trp	Leu 430	Pro	Trp
His	G1n	G1u 435	Asn	Gly	Pro	Ala	Gly 440	Pro	Val	Pro	Ser	Phe 445	Leu	Gly	Arg
Ser	Pro 450	Met	His	Arg	Val	Thr 455	Leu	Gln	Glu	Val	Leu 460	Thr	Leu	Leu	Pro
Asn 465	Ser	Met	Ala	Leu	Leu 470	Leu	Gln	Lys	Glu	Pro 475	Trp	Lys	G1u	Gln	Thr 480
G1n	Lys	Phe	Пе	Asp 485	Trp	Leu	Phe	Ser	Ile 490	Met	Glu	Ser	Pro	Lys 495	
Ala	Leu	Ser	A1a 500	Gln	Ser	Arg	Asp	Leu 505	Leu	Lys	Ala	Thr	Leu 510		Ser
Leu	Arg	Val 515		Pro	Glu	Phe	Lys 520		Lys	Ala	Va1	Trp 525	Thr	Arg	Ala
Tyr	Gly 530														

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	tgg Trp	_		_					_			 _	-	_	240
	tca Ser														288
	ggc Gly														336
	gcc Ala	_				_			-	-		-		_	384
	gcc Ala 130														432

	Val					Pro					Glu				gag Glu 160	480
						ctt Leu									tcc Ser	528
						gaa Glu										576
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Ala	Val	Va1 35		Pro	Gly	Phe	Leu 40		Thr	Ala	Glu	G1u 45		Thr	Leu	
Ser	Arg 50		Leu	Glu	Pro	G1u 55		Arg	Arg	Arg	Arg 60	Tyr	Glu	Tyr	Asp	
His 65	Trp	Asp	Ala	Ala	11e 70	His	Gly	Phe	Arg	G1u 75	Thr	Glu	Lys	Ser	Arg 80	
Trp	Ser	Glu	Ala	Ser 85	Arg	Ala	Ile	Leu	G1n 90	Arg	Val	Gln	Ala	Ala 95	Ala	
Phe	Gly	Pro	Gly 100	Gln	Thr	Leu	Leu	Ser 105	Ser	Val	His	Val	Leu 110		Leu	
Glu	Ala	Arg 115	Gly	Tyr	Пe	Lys	Pro 120		Val	Asp	Ser	Ile 125		Phe	Cys	
Gly	Ala		Пe	Ala	Gly	Leu		Leu	Leu	Ser	Pro		Val	Met	Arg	

	130					135					140					
Leu 145	Val	His	Thr	Gln	Glu 150	Pro	Gly	Glu	Trp	Leu 155	Glu	Leu	Leu	Leu	Glu 160	
Pro	Gly	Ser	Leu	Tyr 165	Пe	Leu	Arg	Gly	Ser 170	Ala	Arg	Tyr	Asp	Phe 175	Ser	
His	Glu	Ile	Leu 180	Arg	Asp	Glu	Glu	Ser 185	Phe	Phe	Gly	Glu	Arg 190	Arg	Ile	
Pro	Arg	Gly 195	Arg	Arg	Пe	Ser	Va1 200	Пe	Cys	Arg	Ser	Leu 205	Pro	Glu	Gly	
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_	-					gat Asp			-					_	-	96
						act Thr			-	-	-		_		-	144
						ttg Leu 55										192
			_		_	gac Asp				-		-	-	_		240
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482

85 90 95

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Ala Asp Ser Ser Ile Phe Asp Ser Lys Val Thr Glu Ile Ser Lys Glu 25

Asn Leu Leu Ile Gly Ser Thr Ser Tyr Val Glu Glu Glu Met Pro Gln 40

Ile Glu Thr Arg Val Ile Leu Val Gln Glu Ala Gly Lys Gln Glu Glu 55 60

Leu Ile Lys Ala Leu Lys Asp Ile Lys Val Gly Phe Val Lys Met Glu 70 75 Ser Val Glu Glu Phe Glu Gly Leu Asp Ser Pro Glu Phe Glu Met Tyr 90

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Leu

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48

96

ttc tgc ctc ctg tgg ccc ctc gtg gtg aag ggc tgc acg atg atc cgg Phe Cys Leu Leu Trp Pro Leu Val Val Lys Gly Cys Thr Met Ile Arg

			20					25					30			
						att Ile										144
						agc Ser 55										192
						agg Arg										240
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Phe	Cys	Leu	Leu 20	Trp	Pro	Leu	Val	Va1 25	Lys	Gly	Cys	Thr	Met 30	Ile	Arg	
Trp	Lys	Ile 35	Asn	Asn	Leu	Ile	A1a 40	Ser	Glu	Ser	Tyr	Tyr 45	Thr	Tyr	Ala	
Ser	I1e 50	Ser	Gly	He	Ser	Ser 55	Met	Pro	Ser	Leu	Arg 60	His	Ser	Arg	Met	
G1y 65	Ser	Met	Phe	Ser	Ser 70	Arg	Met	Thr	Glu	Asp 75		Ala	Glu		Lys 80	
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1 5 10 15

cgt gtt tat cct tcc tgc ctt gaa cct ggt cag agt ttt att act gag 96 Arg Val Tyr Pro Ser Cys Leu Glu Pro Gly Gln Ser Phe Ile Thr Glu 20 25 30

gaa gat gat gca cgg agt gag tct agt act gaa tgg gac tta gat gga 144 Glu Asp Asp Ala Arg Ser Glu Ser Ser Thr Glu Trp Asp Leu Asp Gly 35 40 45

ttc agt gag ctg gac tct gag tca gga agt tca agt tct ttt tca gat
Phe Ser Glu Leu Asp Ser Glu Ser Gly Ser Ser Ser Ser Phe Ser Asp
50 55 60

gat gaa gtc tgg gtg caa gta gca cct cag cga aat gca cag gat cag
Asp Glu Val Trp Val Gln Val Ala Pro Gln Arg Asn Ala Gln Asp Gln
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cag ggt tct ttg taa 255 Gln Gly Ser Leu *

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Arg Val Tyr Pro Ser Cys Leu Glu Pro Gly Gln Ser Phe Ile Thr Glu 20 25 30

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Phe Ser Glu Leu Asp Ser Glu Ser Gly Ser Ser Ser Phe Ser Asp 50 55 60

Asp Glu Val Trp Val Gln Val Ala Pro Gln Arg Asn Ala Gln Asp Gln

485

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		cgt Arg 35								_	_	-		-	144
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tag *															243

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<211> 80

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Αla	Leu	Arg 35	Phe	Leu	Asn	His	Leu 40	Thr	Ser	Phe	Lys	Glu 45	Ser	Tyr	Glu	
Thr	G1n 50	Met	Asn	Met	Leu	Tyr 55	Ser	Gln	Leu	Val	Glu 60	Ala	Leu	Ser	Asn	
Asn 65	Lys	Gly	Pro	Val	Phe 70	His	Glu	His	Gly	Tyr 75	Trp	Ser	Lys	Ser	Asp 80	
	<br </td <td>210> 211> 212> 213></td> <td>237 Dna</td> <td>o sa;</td> <td>oiens</td> <td>S</td> <td></td>	210> 211> 212> 213>	237 Dna	o sa;	oiens	S										
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													gtg Val			48
									_		_		gta Val 30	_	_	96
													ccg Pro			144
													ctg Leu	_	_	192
						tat Tyr							gac Asp	tga *		237

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<211> 78 <212> PRT <213> Homo sapiens <400> 336 Met Pro Val Val Leu Ser Gln Glu Val Glu Ser Val Leu Val Gly Ala 10 Ala Val Leu Gly Ala Cys Ala Ser Gly Asp Phe Ala Ser Val Gln Glu Ala Met Ala Lys Met Ser Lys Val Gly Lys Val Val Phe Pro Arg Leu 40 45 Gln Asp Lys Lys Tyr Tyr Asp Lys Lys Tyr Gln Val Phe Leu Lys Leu 55 Val Glu His Gln Lys Glu Tyr Leu Ala Ile Met Asn Asp Asp 65 70 75 <210> 337 <211> 567 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(567) <400> 337 atg cac tot att otg gat att att got gga tto ota tat acc att tta 48 Met His Ser Ile Leu Asp Ile Ile Ala Gly Phe Leu Tyr Thr Ile Leu 1 atc tta gct gtc ttc tat cca ttt gtg gac ctg att gac aac ttc aac 96 Ile Leu Ala Val Phe Tyr Pro Phe Val Asp Leu Ile Asp Asn Phe Asn 20 25 30 caa act cac aaa tat gct cca ttc atc atc atc ggg ctt cat tta gct 144 Gln Thr His Lys Tyr Ala Pro Phe Ile Ile Ile Gly Leu His Leu Ala 35 40 192 ttg ggg atc ttt tct ttc act ctt gac acc tgg agc aca tcc cga gga Leu Gly Ile Phe Ser Phe Thr Leu Asp Thr Trp Ser Thr Ser Arg Gly 50 55 60 gac aca gcc gag ata cta gga agt ggt gct gga att gca tgt gga tct 240 Asp Thr Ala Glu Ile Leu Gly Ser Gly Ala Gly Ile Ala Cys Gly Ser

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65 70 75 80 cat gtt act tat aac atg ggt cta gta tta gat cct tct cta gat aca 288 His Val Thr Tyr Asn Met Gly Leu Val Leu Asp Pro Ser Leu Asp Thr 85 95 tta cct tta gct ggg ccc ccc att act gtg act ctg ttt gga aaa gcc. 336 Leu Pro Leu Ala Gly Pro Pro Ile Thr Val Thr Leu Phe Gly Lys Ala 100 105 110 384 ata ttg cgg atc ctc ata ggg atg gta ttt gta cta ata atc aga gat Ile Leu Arg Ile Leu Ile Gly Met Val Phe Val Leu Ile Ile Arg Asp 125 115 120 gta atg aaa aag atc acc att cct tta gcc tgc aaa atc ttc aat ata 432 Val Met Lys Lys Ile Thr Ile Pro Leu Ala Cys Lys Ile Phe Asn Ile 140 130 135 ccq tgt gat gat att cga aaa gca aga cag cac atg gaa gtt gaa ctt 480 Pro Cys Asp Asp Ile Arg Lys Ala Arg Gln His Met Glu Val Glu Leu 150 cct tat cgg tat att acc tat gga atg gtt ggt ttc tcc atc aca ttt 528 Pro Tyr Arg Tyr Ile Thr Tyr Gly Met Val Gly Phe Ser Ile Thr Phe 165 170 175 ttt gtt cct tac ata ttt ttc ttt att ggt atc tct tga 567 Phe Val Pro Tyr Ile Phe Phe Phe Ile Gly Ile Ser * 180 185 <210> 338 <211> 188 <212> PRT <213> Homo sapiens <400> 338 Met His Ser Ile Leu Asp Ile Ile Ala Gly Phe Leu Tyr Thr Ile Leu Ile Leu Ala Val Phe Tyr Pro Phe Val Asp Leu Ile Asp Asn Phe Asn 25 20 Gln Thr His Lys Tyr Ala Pro Phe Ile Ile Gly Leu His Leu Ala 40 Leu Gly Ile Phe Ser Phe Thr Leu Asp Thr Trp Ser Thr Ser Arg Gly

	50				•	55					60					
Asp 65	Thr	Ala	Glu	Пe	Leu 70	Gly	Ser	Gly	Ala	G1y 75	Ile	Ala	Cys	Gly	Ser 80	
His	۷a٦	Thr	Tyr	Asn 85	Met	Gly	Leu	۷a۱	Leu 90	Asp	Pro	Ser	Leu	Asp 95		
Leu	Pro	Leu	Ala 100		Pro	Pro	Ile	Thr 105		Thr	Leu	Phe	Gly 110		Ala	
Ile	Leu	Arg 115		Leu	Пe	Gly	Met 120		Phe	۷a۱	Leu	Ile 125		Arg	Asp	
Val	Met 130	Lys	Lys	IJе	Thr	Ile 135		Leu	Ala	Cys	Lys 140		Phe	Asn	Ile	
Pro 145			Asp	Ile	Arg 150	Lys	Ala	Arg	Gln	His 155		Glu	Val	Glu	Leu 160	
	Tyr	Arg	Tyr	Ile 165		Tyr	Gly	Met	Val 170		Phe	Ser	Ile	Thr 175		
Phe	Val	Pro	Tyr 180		Phe	Phe	Phe	Ile 185		Ile	Ser					
	<'a	210> 211> 212> 213>	210	o sap	oiens	5										
	<2	220> 221> 222>	CDS (1).	(2	210)											
		100>														40
_	-				_	ggg Gly			_	-	_	-			-	48
_				_		gtc Val	_		-							96
						gcg Ala				-						144
						gtg Val 55										192

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tac cta acc att ctt taa
                                                                       210
Tyr Leu Thr Ile Leu *
 65
      <210> 340
      <211> 69
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      <213> Homo sapiens
      <400> 340
Met Val Ser His Phe Met Gly Ser Leu Ser Val Leu Cys Phe Leu Leu
                 5
 1
                                     10
                                                         15
Leu Leu Gly Phe Gln Phe Val Cys Pro Gln Pro Ser Thr Gln His Arg
                                 25
Lys Val Pro Gln Arg Met Ala Ala Glu Gly Ala Pro Glu Asp Asp Gly
Gly Gly Gly Ala Pro Gly Val Trp Gly Ala Gly Ala Pro Ala Glu Gly
    50
                        55
                                             60
Tyr Leu Thr Ile Leu
65
      <210> 341
      <211> 225
      <212> DNA
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      <220>
      <221> CDS
      <222> (1)...(225)
      <400> 341
atg ccg gct aag gac aca agt tca gtg ttt gcc ctg gct tgt agc cca
                                                                       48
Met Pro Ala Lys Asp Thr Ser Ser Val Phe Ala Leu Ala Cys Ser Pro
                 5
 1
                                      10
                                                          15
gcg ggg gct ccg tca tcc cct ggg gaa tgc ctc ggc ctg caa gac cgc
                                                                       96
Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg
             20
                                 25
ata ccg cat tgg aac agg gaa acc acc tac ttc agc acc tcc ctc agc
                                                                      144
Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser
         35
                             40
                                                  45
```

```
aag gtg gca ggt ccc aac aag cct tgc acc acg agg aag tgg cag tgg
                                                                      192
Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp
     50
                         55
                                              60
cat tog gga tat ggc toc otg gcc agc ttg tga
                                                                      225
His Ser Gly Tyr Gly Ser Leu Ala Ser Leu *
 65
                     70
      <210> 342
      <211> 74
      <212> PRT
      <213> Homo sapiens
      <400> 342
Met Pro Ala Lys Asp Thr Ser Ser Val Phe Ala Leu Ala Cys Ser Pro
                                    10
Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg
                                25
Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser
                            40
Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp
                        55
His Ser Gly Tyr Gly Ser Leu Ala Ser Leu
65
                    70
      <210> 343
      <211> 240
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(240)
      <400> 343
atg tgc atc acg cac ctg gac cac aaa gac tac atc ttc ctg ctg ctc
                                                                       48
Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu
 1
                                     10
atc ggc ttc tgc atc ttc gcc gcg gga act gtg gct gcc tgg ctc aca
                                                                       96
Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr
             20
                                 25
```

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ggt gtg tgt gct gtg ctc tac cag aac acc cgc cac aag tcg agt gaa 144 Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu 35 40 45 gaa gat gag gac gag gcc ggg act agg gtg gaa gtc agc cgg cgg att 192 Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile 50 55 ttt caa acc cag acg agc tcg gtc cag gag ttc cct cag ctt att tag 240 Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile * 65 70 75 <210> 344 <211> 79 <212> PRT <213> Homo sapiens <400> 344 Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu 5 10 Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr 25 Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile 55 Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile 70 <210> 345 <211> 285 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(285) <400> 345 atg act gcc aag gac tgc tcc atc atg att gca ctg tct ccc tgt ctg 48 Met Thr Ala Lys Asp Cys Ser Ile Met Ile Ala Leu Ser Pro Cys Leu 1 10 15

					caa Gln						_		96
	_				tct Ser				-		_		144
 -					tat Tyr 55				_		-		192
			-	-	gcc Ala	_		-		_	_		 240
_	_	-	-	_	tgc Cys		-			_	-	taa *	285

<210> 346

<211> 94

<212> PRT

<213> Homo sapiens

<400> 346

Met Thr Ala Lys Asp Cys Ser Ile Met Ile Ala Leu Ser Pro Cys Leu 1 5 10 15 Gln Asp Ala Ser Ser Asp Gln Arg Pro Val Val Pro Ser Ser Arg Ser 20 25 30 Arg Phe Ala Phe Ser Val Ser Val Leu Asp Leu Asp Leu Lys Pro Tyr

Arg Phe Ala Phe Ser Val Ser Val Leu Asp Leu Asp Leu Lys Pro Tyr
35 40 45

Glu Ser Ile Pro His Gln Tyr Lys Leu Asp Gly Lys Ile Val Asn Tyr 50 55 60

Tyr Ser Lys Thr Val Arg Ala Lys Asp Asn Ala Val Met Ser Thr Arg 65 70 75 80

Phe Lys Glu Ser Glu Asp Cys Thr Leu Val Leu His Lys Val 85 90

<210> 347

<211> 474

<212> DNA

<213> Homo sapiens

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	gag		ctg			gcc Ala				-		-	_			48
-		_				cgc Arg				-		-		_	-	96
						cat His					-	_	-			144
			-			tac Tyr 55	-	-	-	_		-	_			192
	-					ccg Pro	_							_	-	240
-			-			ttc Phe		_			-		_	_		288
	-	_	_	-		cag Gln		-	Phe		_			_	•	336
						act Thr										384
						act Thr 135										432
_						gaa Glu	-	_		_	_		tga *			474

495

145 150 155 <210> 348 <211> 157 <212> PRT <213> Homo sapiens <400> 348 Met Glu Ala Leu Arg Arg Ala His Glu Val Ala Leu Arg Leu Leu Leu 5 10 Cys Arg Pro Trp Ala Ser Arg Ala Ala Ala Arg Pro Lys Pro Ser Ala Ser Glu Val Leu Thr Arg His Leu Leu Gln Arg Arg Leu Pro His Trp Thr Ser Phe Cys Val Pro Tyr Ser Ala Val Arg Asn Asp Gln Phe Gly 55 Leu Ser His Phe Asn Trp Pro Val Gln Gly Ala Asn Tyr His Val Leu 75 Arg Thr Gly Cys Phe Pro Phe Ile Lys Tyr His Cys Ser Lys Ala Pro 90 Trp Gln Asp Leu Ala Arg Gln Asn Arg Phe Phe Thr Ala Leu Lys Val 105 Val Asn Leu Gly Ile Pro Thr Leu Leu Tyr Gly Leu Gly Ser Trp Leu 125 120 Phe Ala Arg Val Thr Glu Thr Val His Thr Ser Tyr Gly Pro Ile Thr 130 135 140 Val Tyr Phe Leu Asn Lys Glu Asp Glu Gly Ala Met Tyr 150 <210> 349 <211> 288 <212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)...(288)

<400> 349

atg gcg aaa gca ctg att gtc att ttt agc agt cac tta agg cct ata Met Ala Lys Ala Leu Ile Val Ile Phe Ser Ser His Leu Arg Pro Ile 1 5 10

ctt Leu										96
tcg Ser										144
cac His 50										192
aca Thr										240
aac Asn			 _			-	•	tga *	;	288

<210> 350

<211> 95

<212> PRT

<213> Homo sapiens

<400> 350

 Met
 Ala Lys
 Ala Leu Ile
 Val
 Ile
 Phe
 Ser
 Ser
 His
 Leu Arg
 Pro
 Ile

 Glu
 Leu Phe
 Ser
 Ser
 Arg
 Lys
 Val
 Leu Phe
 Leu Leu Ser
 Gln
 Lys
 Trp

 Ala
 Ser
 Asn
 Asn
 Asn
 Gln
 Ser
 Arg
 Ser
 Val
 Ala
 Val
 Gly
 Lys
 Met
 Val
 Asp
 Asp
 Glu
 Trp
 Asn
 Cys

 Arg
 His
 Gln
 Ser
 Tyr
 Phe
 Leu
 Ile
 Cys
 Pro
 Val
 Ala
 Val
 Asp
 Glu
 Trp
 Asn
 Cys

 Asn
 Thr
 Ser
 Asp
 Val
 Glu
 Leu
 Met
 Gly
 Ala
 Thr
 Ala
 Val
 Gln
 Thr
 Ile

 Asn
 Thr
 His
 Ser
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 Gly
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 Met
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 Thr
 Ala
 Val
 Gln
 Thr
 Ile

 Asn
 Asn
 Thr</td

90

<210> 351

<211> 165

<212> DNA

<213> Homo sapiens

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      <222> (1)...(165)
      <400> 351
atq tqc tcc atc ccc cgg cat ctg ctg cca ttg gtc ctg cct gtt gcg
                                                                      48
Met Cys Ser Ile Pro Arg His Leu Leu Pro Leu Val Leu Pro Val Ala
                 5
                                     10
tta ctt ctc tgt gcc ctg gag ccc ctc aag cac aga ggc ctc gaa agg
                                                                      96
Leu Leu Cys Ala Leu Glu Pro Leu Lys His Arg Gly Leu Glu Arg
             20
                                 25
ttg atc aga cat cct cag cac ctg gag cgg ggc ctg gca cac aag acg
                                                                     144
Leu Ile Arg His Pro Gln His Leu Glu Arg Gly Leu Ala His Lys Thr
         35
                             40
                                                 45
gca atg aac ggc caa ccc tag
                                                                     165
Ala Met Asn Gly Gln Pro *
     50
      <210> 352
      <211> 54
      <212> PRT
      <213> Homo sapiens
      <400> 352
Met Cys Ser Ile Pro Arg His Leu Leu Pro Leu Val Leu Pro Val Ala
Leu Leu Cys Ala Leu Glu Pro Leu Lys His Arg Gly Leu Glu Arg
                               25
Leu Ile Arg His Pro Gln His Leu Glu Arg Gly Leu Ala His Lys Thr
        35
                            40
                                                45
Ala Met Asn Gly Gln Pro
    50
      <210> 353
      <211> 159
      <212> DNA
      <213> Homo sapiens
      <220>
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<221> CDS
      <222> (1)...(159)
      <400> 353
atg tgc ttg agg gtt ttc acc ctg gcc ctc agt tgc ctg tgc ggg
                                                                       48
Met Cys Leu Arg Val Phe Thr Leu Ala Leu Ser Cys Leu Leu Cys Gly
tcc ctg ggg cag ctg cag ggg ctc acg gac cca tca ggg tct cca cag
                                                                       96
Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
             20
                                 25
ctc ccc tgc agt gtg tgc acc cca caa tgt ctg cgg ctc ttc ttc cgg
                                                                      144
Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
         35
cgt gtc ggg ctt tga
                                                                      159
Arg Val Gly Leu *
     50
      <210> 354
      <211> 52
      <212> PRT
      <213> Homo sapiens
      <400> 354
Met Cys Leu Arg Val Phe Thr Leu Ala Leu Ser Cys Leu Leu Cys Gly
                 5
                                    10
Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
                                25
                                                    30
Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
                            40
        35
                                                45
Arg Val Gly Leu
   50
     <210> 355
     <211> 210
     <212> DNA
     <213> Homo sapiens
     <220>
     <221> CDS
     <222> (1)...(210)
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	ggt Gly		atg													48
	tta Leu															96
	atg Met		-									_				144
-	cta Leu 50	_	-		_	-	_		_		-			-		192
	gaa Glu			-	tag *			•								210
	<2 <2	210> 211> 212> 213>	69	sap	oiens	5		•								
Ma+		100>		۸۵۵	Hiso	Acn	The	۸۵۵	Tun	200	Dha	Cl.	V-1	Cl.	Cua	
1	Gly			5					10					15		,
Gly	Leu	Ile	Va1 20	Val	Ala	Tyr	Lys	Asp 25	Gly	Ser	Pro	Ala	His 30	Pro	His	
Phe	Met	Asp 35	Ala	Glu	Leu	Cys	Ser 40	G1n	Tyr	Trp	Thr	Lys 45	Trp	Leu	Leu	
Arg	Leu 50		Glu	Tyr	Thr	G1u 55	Lys	Lys	Lys	Asn	Gln 60		Ile	Gln	Lys	
Pro 65	Glu	Tyr	Ser	Glu	٠			-			00					
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500

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      <221> misc feature
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atg gtc ctg ccg gtg gca gcc tat ggn ctg atc ctg atg gcc atg ctg
                                                                       48
Met Val Leu Pro Val Ala Ala Tyr Xaa Leu Ile Leu Met Ala Met Leu
1
                                                         15
tgg cgc ggc ctg gcc cag ggc ggg agt gcc ggc tgg ggc gcg ctg ctc
                                                                       96
Trp Arg Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu
             20
                                 25
ttc acg ctc tct gat ggc gtg ctg gcc tgg gac acc ttc gcc cag ccc
                                                                      144
Phe Thr Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro
         35
                             40
ctg ccc cat gcc cgc ctg gtg atc atg acc acc tac tat gct gcc cag
                                                                      192
Leu Pro His Ala Arg Leu Val Ile Met Thr Thr Tyr Tyr Ala Ala Gln
    50
                         55
                                             60
                                                                      240
ctc ctc atc aca ctg tca gcc ctc agg agc ccg gtg ccc aag act gac
Leu Leu Ile Thr Leu Ser Ala Leu Arg Ser Pro Val Pro Lys Thr Asp
65
                     70
                                                             80
                                         75
                                                                     243
tga
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<210> 358
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<220>

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<211> 80

<212> PRT

<213> Homo sapiens

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<400> 358 Met Val Leu Pro Val Ala Ala Tyr Xaa Leu Ile Leu Met Ala Met Leu Trp Arg Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu Phe Thr Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro Leu Pro His Ala Arg Leu Val Ile Met Thr Thr Tyr Tyr Ala, Ala Gln 55 60 Leu Leu Ile Thr Leu Ser Ala Leu Arg Ser Pro Val Pro Lys Thr Asp 65 70 75 80 <210> 359 <211> 324 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(324) <400> 359 atg aag agc acc tgt ggt tcc ctt gtg gcc atg agt gtt gtg gga 48 Met Lys Ser Thr Cys Gly Ser Leu Val Ala Met Ser Val Val Gly 5 10 cca gca tca ago gca aga gat ctg ccg agt cca cgt gga tac act atg 96 Pro Ala Ser Ser Ala Arg Asp Leu Pro Ser Pro Arg Gly Tyr Thr Met 20 25 30 acc ccg cag acc atg aag gta gat gag gag gta atg gca ttc cqt qqt 144 Thr Pro Gln Thr Met Lys Val Asp Glu Glu Val Met Ala Phe Arg Gly 35 gcc cga tgt gat ggc atc agg gtt ctt cct agc agc gtg gaa gac act 192 Ala Arg Cys Asp Gly Ile Arg Val Leu Pro Ser Ser Val Glu Asp Thr 50 55 60 cct gcc ctc aag agg gct aag tcc agt aaa acc caa cca aca qqa qac 240 Pro Ala Leu Lys Arg Ala Lys Ser Ser Lys Thr Gln Pro Thr Gly Asp 65 70 75 agt tgg gca gga aga ctc att ctg agt gta gat ggc tct ggg ttt tgt 288

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```
Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
                 85
                                                          95
gag agg gtg aaa tot ttg gto gtt aaa caa tto tag
                                                                      324
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe *
            100
                                105
      <210> 360
      <211> 107
      <212> PRT
      <213> Homo sapiens
      <400> 360
Met Lys Ser Thr Cys Gly Ser Leu Val Ala Met Ser Val Val Val Gly
                 5
Pro Ala Ser Ser Ala Arg Asp Leu Pro Ser Pro Arg Gly Tyr Thr Met
                                25
Thr Pro Gln Thr Met Lys Val Asp Glu Glu Val Met Ala Phe Arg Gly
Ala Arg Cys Asp Gly Ile Arg Val Leu Pro Ser Ser Val Glu Asp Thr
                        55
Pro Ala Leu Lys Arg Ala Lys Ser Ser Lys Thr Gln Pro Thr Gly Asp
Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
                                    90
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe
            100
                                105
      <210> 361
      <211> 252
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(252)
      <400> 361
atg gag gaa ggc ggc ggc gta cgg agt ctg gtc ccg ggc ggg ccg
                                                                      48
Met Glu Glu Gly Gly Gly Val Arg Ser Leu Val Pro Gly Gly Pro
1
                                     10
gtg tta ctg gtc ctc tgc ggc ctc ctg gag gcg tcc ggc ggc ggc cga
                                                                      96
```

Val	Leu	Leu	Va1 20	Leu	Cys	Gly	Leu	Leu 25	Glu	Ala	Ser	Gly	Gly 30	Gly	Arg		
				ctc Leu													144
				tct Ser													192
				atg Met			-			-						,	240
	aaa Lys	aac Asn	taa *								,					;	252

<210> 362

<211> 83

<212> PRT

<213> Homo sapiens

<400> 362

<210> 363

<211> 459

<212> DNA

<213> Homo sapiens

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	gat Asp		aca							-		-		-		48
	gga Gly										_					96
	gta Val	-			-		_	-		-					_	144
	gga Gly 50	-				-	_					_	-			192
-	tca Ser			_		-				-				-	-	. 240
	att Ile	-	_	_		_	-			-		_	-			288
	cac His	-					-				-		_	-		336
	999 Gly															384
-	ctg Leu 130			-				_	-				-			432
	gga Gly	-	-				_	tag *								459

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<210> 364
      <211> 152
      <212> PRT
      <213> Homo sapiens
      <400> 364
Met Asp Gly Thr Gln Gln Gln Ile Phe Lys Met Leu Ala Glu Val Leu
Gly Gly Ile Asn Cys Val Lys Ala Ser Val Leu Thr Pro Tyr Tyr His
Lys Val Asp Phe Glu Cys Ile Leu Asp Lys Arg Lys Pro Leu Pro
        35
Tyr Gly Ser His Asn Ile Ala Leu Gly Gln Leu Pro Glu Met Pro Trp
                        55
Glu Ser Asn Ile Glu Ile Val Gly Ser Arg Leu Pro Pro Gly Ala Glu
                    70
                                        75
Arg Ile Ala Leu Glu Phe Leu Asp Ser Lys Ala Leu Cys Arg Asn Ile
                85
                                    90
Pro His Met Lys Gly Lys Ser Ala Met Lys Lys Arg His Leu Glu Ile
            100
                                105
                                                    110
Leu Gly Tyr Arg Val Ile Gln Ile Ser Gln Phe Glu Trp Asn Ser Met
                            120
                                                125
Ala Leu Ser Thr Lys Asp Ala Arg Met Asp Tyr Leu Arg Glu Cys Ile
                        135
                                            140
Phe Gly Glu Val Lys Ser Cys Leu
145
                    150
      <210> 365
      <211> 600
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(600)
      <400> 365
atg gtg tgg cgc cgg ctt ctg cgg aag agg tgg gtg ctc gcc ctg gtc
                                                                       48
Met Val Trp Arg Arg Leu Leu Arg Lys Arg Trp Val Leu Ala Leu Val
 1
                                     10
ttc ggg ctg tcg ctc gtc tac ttc ctc agc agc acc ttc aag cag gag
                                                                       96
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Phe	Gly	Leu	Ser 20	Leu	Val	Tyr	Phe	Leu 25	Ser	Ser	Thr	Phe	Lys 30	Gln	G1u	
														cat His		144
														agt Ser		192
														atc Ile		240
														aat Asn 95		288
												_	_	gat Asp		. 336
														tcc Ser		384
					Lys									aac Asn		432
			-			Asn				_	Val	_	-	cac His		480
-			-	-		-					_	-		cag Gln 175		528
					-		Пe	-			_			gaa Glu	-	576
cca	ccc	aaa	ctc	ttc	ccc	act	taa									600

507 .

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Pro Pro Glu Leu Phe Pro Ala *
        195
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Met Val Trp Arg Arg Leu Leu Arg Lys Arg Trp Val Leu Ala Leu Val
Phe Gly Leu Ser Leu Val Tyr Phe Leu Ser Ser Thr Phe Lys Gln Glu
                                25
Glu Arg Ala Val Arg Asp Arg Asn Leu Leu Gln Val His Asp His Asn
Gln Pro Ile Pro Trp Lys Val Gln Phe Asn Leu Gly Asn Ser Ser Arg
                        55
                                            60
Pro Ser Asn Gln Cys Arg Asn Ser Ile Gln Gly Lys His Leu Ile Thr
Asp Glu Leu Gly Tyr Val Cys Glu Arg Lys Asp Leu Leu Val Asn Gly
                                    90
Cys Cys Asn Val Asn Val Pro Ser Thr Lys Gln Tyr Cys Cys Asp Gly
                                105
Cys Trp Pro Asn Gly Cys Cys Ser Ala Tyr Glu Tyr Cys Val Ser Cys
                            120
Cys Leu Gln Pro Asn Lys Gln Leu Leu Leu Glu Arg Phe Leu Asn Arg
                        135
                                            140
Ala Ala Val Ala Phe Gln Asn Leu Phe Met Ala Val Glu Asp His Phe
                    150
                                        155
Glu Leu Cys Leu Ala Lys Cys Arg Thr Ser Ser Gln Ser Val Gln His
                                    170
Glu Asn Thr Tyr Arg Asp Pro Ile Ala Lys Tyr Cys Tyr Gly Glu Ser
            180
                                185
Pro Pro Glu Leu Phe Pro Ala
        195
      <210> 367
      <211> 249
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      <220>
      <221> CDS
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508

<222> (1)...(249)

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agt gga tga Ser Gly *

<210> 368 <211> 82

<212> PRT

<213> Homo sapiens

<400> 368

 Met Ser Lys
 Tyr
 Lys
 His
 Lys
 Ser
 Ser
 Pro
 Leu
 Leu
 Pro
 Leu
 Leu
 Pro
 Leu
 Leu
 Pro
 Leu
 Leu
 Ala
 Asn
 Lys
 Pro
 Leu
 Ala
 Ala
 Cys
 Leu
 Glu
 Ser
 Glu
 Asn
 Ala
 Ala
 Ala
 Ala
 Cys
 Leu
 Glu
 Ser
 Glu
 Asn
 Asn
 Ala
 Ala
 Ala
 Leu
 Gly
 Ser
 Asp
 Leu
 Gln
 Asn
 Asn
 Ser
 Pro
 Ile
 Ile
 Ile
 Ile
 Ala
 Ala
 Ala
 Leu
 Gly
 Ser
 Asp
 Leu
 Gln
 Asn
 Ala
 Ala
 Ala
 Leu
 Gly
 Ser
 Asp
 Leu
 Gln
 Asp
 Ile
 Gln
 Asp
 Ala
 Ala
 Ala
 Leu
 Gly
 Ser
 Asp
 Leu
 Gln
 Asp
 Asp
 Asp
 Pro
 Ile
 Ser
 Leu
 Gln
 Asp
 Asp
 Asp
 Asp
 Pro
 Ile

509

Ser Gly

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<210> 370

<211> 94

<212> PRT

<213> Homo sapiens

<400> 370

510

Met Asp Gly Arg Gly Ala Phe Trp Thr Val Ala Ile Pro Arg Ala Arg Gln Glu Gly Leu Gly Arg Leu Gly Leu Pro Phe Pro Val Lys Arg Thr 25 Pro Pro Ala Pro Gln Asn Pro Gly Gly Ser Thr Gln Ala Pro Gln Arg Val Val Gly Lys Ser His Ser Gly Ile Arg Met Pro Ala Lys Ser Arg 55 Asn Leu Arg Leu Glu Ser Lys Leu Asn Arg Thr Ala Val Cys Glu Ala 65 80 Leu Lys Arg Ala Pro Thr Thr Asn Leu Pro Gly Val Gly Ser 90 <210> 371 <211> 249 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(249) <400> 371 atg cgc gac tgc gac atc aac gac gac gaa ttc ctg cac ctg ccg gcg 48 Met Arg Asp Cys Asp Ile Asn Asp Asp Glu Phe Leu His Leu Pro Ala 1 10 15 96 cat ttg cgg qtg qtc qgg ccc cag cag ctg cat tcc gag acc aac gag His Leu Arg Val Val Gly Pro Gln Gln Leu His Ser Glu Thr Asn Glu 20 30 25 cgg ctc ttc gat gag aag tac aag cct gtc gtg ctc acc gac gat cag 144 Arg Leu Phe Asp Glu Lys Tyr Lys Pro Val Val Leu Thr Asp Asp Gln gtg gac cag gcg ctg tgg gag gag cag gtc ttg cag aag gag aag aag 192 Val Asp Gln Ala Leu Trp Glu Glu Gln Val Leu Gln Lys Glu Lys Lys 50 55 60 gac agg ctc gcc ctg agc cag gcc cac tcg ctg gtg cag gcg gag gcc 240 Asp Arg Leu Ala Leu Ser Gln Ala His Ser Leu Val Gln Ala Glu Ala 65 70 75 ccg aga tga 249

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511

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Pro Arg *
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<210> 372 <211> 82 <212> PRT <213> Homo sapiens

<400> 372

 Met Arg Asp Asp Asp Asp Ile Asn Asp Asp Glu Phe Leu His Leu Pro Ala 1

 1
 5
 10
 15
 15

 His Leu Arg Val Val 20
 Pro Gln Gln Leu His Ser Glu Thr Asn Glu 30
 30

 Arg Leu Phe Asp Glu Lys Tyr Lys Pro Val Val Leu Thr Asp Asp Gln 35
 40
 45

 Val Asp Gln Ala Leu Trp Glu Glu Glu Gln Val Leu Gln Lys Glu Lys Lys 50
 55
 60

 Asp Arg Leu Ala Leu Ser Gln Ala His Ser Leu Val Gln Ala Glu Ala 65
 70
 75
 80

 Pro Arg

<210> 373 <211> 219 <212> DNA

<213> Homo sapiens

<220> <221> CDS

<222> (1)...(219)

<221> misc_feature
<222> (1)...(219)

<223> n = A.T.C or G

<400> 373

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nga gcg can gca gca ggc tcc att ccc ggc cgc cgc cgc cgc tca gcc cat
Xaa Ala Xaa Ala Ala Gly Ser Ile Pro Gly Arg Arg Arg Ser Ala His
20 25 30

```
tac gca aac ctg gcg ggt cca acc aac ccc gct ctg ccg ccg ctg ctg
                                                                     144
Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu
        35
                             40
                                                 45
gaa ccc agg agg cgt gct tgc agg ctt cgg gca cta cgc ggg gct gga
                                                                     192
Glu Pro Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly
    50
                         55
aat acc acg cac tgc ccc ttc gcc tag
                                                                     219
Asn Thr Thr His Cys Pro Phe Ala *
 65
                     70
      <210> 374
      <211> 72
     <212> PRT
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Xaa Ala Xaa Ala Ala Gly Ser Ile Pro Gly Arg Arg Arg Ser Ala His
                                25
           20
Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu
                            40
Glu Pro Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly
Asn Thr Thr His Cys Pro Phe Ala
65
                    70
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     <211> 579
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     <222> (1)...(579)
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		gtg Val 20												96
		gct Ala								-	_	_		144
		gcc Åla												192
Trp		gcc Ala							_	_		-		240
		aat Asn			-		_		-		_			288
		ctg Leu 100											_	336
		ggt Gly	_	_	-	-	 	-	-					384
		gtc Val												432
		gtg Val												480
		ccg Pro												528

514

agc tgg gct tac tgc cgg gcc ctg cat aca cag cgc ctc cag tgg gag
Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu
180 185 190

tga 576

<210> 376 <211> 192 <212> PRT

<213> Homo sapiens

<400> 376

10 Val Leu Gly Val Val Ser Leu His Ala Ala Val Ser Thr Ala Glu Ala Ser Arg Gly Ala Ala Ala Gly Phe Leu Leu Gln Val Leu Ala Ala Thr Thr Thr Leu Ala Pro Gly Leu Ser Thr His Glu Asp Cys Leu Ala Gly Ala Trp Val Ala Thr Val Ile Gly Leu Pro Leu Leu Ala Phe Asp Phe 70 75 His Trp Val Asn Gly Asp Arg Ser Ser Ala Asn Leu Leu Gly Gly 90 Gly Met Val Leu Ala Val Ala Gly Gly His Leu Gly Pro Glu Gly Arg 105 Ser Val Ala Gly Gln Ala Met Leu Leu Val Val Ala Val Thr Ile Leu 120 Ile Val Ala Val Phe Thr Ala Asn Thr Tyr Gly Met Trp Gly Gly Ala 135 140 Met Leu Gly Val Ala Gly Leu Leu Ser Arg Leu Glu Glu Asp Arg Leu 145 150 155 Leu Leu Leu Pro Lys Glu Asp Val Cys Arg Trp Ala Leu Ala Val Gly 165 170 Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu 180 185 190

Met Ala Pro Lys Pro Gly Ala Glu Trp Ser Thr Ala Leu Ser His Leu

<210> 377 <211> 606

			DNA Homo	o sap	oiens	5							
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										_	gtg Val		96
											agg Arg		144
											gcc Ala		192
											ggc Gly		240
	-	-			_	_					cag Gln 95		288
											acc Thr	•	336
											ctg Leu		384
											caa Gln		432

	Ser					atc Ile										480
						tgg Trp										528
						gca Ala										576
			Thr			ccc Pro			tga *							606
	<; <;	210> 211> 212> 213>	201	o sap	oiens	5										
Met 1		400> Val		Arg 5	Leu	Val	Ala	Ala	Ala 10	Val	Leu	Val	Ala	Leu 15	Val	
_	Leu	Пе	Leu 20	_	Asn	Val	Ala	A1 a 25		Thr	Ser	Asn	Trp 30		Cys	
Gln	Thr	Leu 35		Asp	Gly	Arg	Arg 40		Ser	Val	Gly	Leu 45		Arg	Ser	•
Cys	Trp 50	Leu	Val	Asp	Arg	Thr 55	Arg	Gly	Gly	Pro	Ser 60	Pro	Gly	Ala	Arg	
65					70	His				75					80	
Glu	Ala	Ala	Gly	Phe 85	Gln	Glu	Ser	Arg	Gly 90	Thr	Val	Lys	Leu	G1n 95	Phe	
Asp	Met	Mẹt	Arg 100	Ala	Cys	Asn	Leu	Val 105	Ala	Thr	Ala	Ala	Leu 110	Thr	Ala	
Gly	Gln	Leu 115	Thr	Phe	Leu	Leu	Gly 120	Leu	Val	Gly	Leu	Pro 125	Leu	Leu	Ser	
Pro	•		Pro	Cys	Trp	Glu 135		Ala	Met	Ala	Ala 140		Phe	Gln	Leu	
	130					TOO										
Ala 145	130 Ser	Phe	Val	Leu	Val 150	Ile	Gly	Leu	Val	Thr 155		Tyr	Arg	Ile	Gly 160	

				165					170					175		
Leu	Leu	Ala	Thr 180		Ala	Ala	Ala	Cys 185		Ser	Gly	Thr	Phe 190		Thr	
Arg	Gly	Arg 195	Thr	Ala	Trp	Pro	Pro 200	Gly								
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		212> 213>	Homo	sap	oiens	Š										
	<2	220> 221> 222>	CDS	(2	297)											
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_	gnc	-	379 acg Thr	_						_	-				_	48
	_		aga Arg 20	_		-						_	-		-	96
			aaa Lys													144
			gga Gly	-	_	-	_	_	-	-	_		-			192
-			cag Gln		-	-							-			240
			agt Ser													288

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act ggt tag
                                                                      297
Thr Gly *
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      <211> 98
      <212> PRT
      <213> Homo sapiens
      <220>
      <221> VARIANT
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      <400> 380
Met Xaa Xaa Thr Leu Val Val Ile Cys Thr Ala Val Ile Val Val
                 5
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Ala Leu Thr Arg Lys Lys Ala Leu Arg Ile His Ser Val Glu Gly Asp
Leu Arg Arg Lys Ser Ala Gly Gln Glu Glu Trp Ser Pro Ser Ala Pro
Ser Pro Pro Gly Ser Cys Val Gln Ala Glu Ala Ala Pro Ala Gly Leu
                        55
Cys Gly Glu Gln Arg Gly Glu Asp Cys Ala Glu Leu His Asp Tyr Phe
                                        75
Asn Val Leu Ser Tyr Arg Ser Leu Gly Asn Cys Ser Phe Phe Thr Glu
                                    90
Thr Gly
      <210> 381
      <211> 264
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(264)
      <400> 381
                                                                      48
atg gct gtc tta gta ctt cgc ctg aca gtt gtc ctg gga ctg ctt gtc
Met Ala Val Leu Val Leu Arg Leu Thr Val Val Leu Gly Leu Leu Val
1
                                     10
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<211> 225 <212> DNA

						gca Ala			Lys								96
						aaa Lys]	144
						gag Glu 55										1	192
						agc Ser										2	240
-			cat His			aag Lys	tga *									2	264
	<2 <2	210> 211> 212> 213>	87	sap	oiens	5											
Met.		100> Val		Val	Leu	Arg	Leu	Thr	Val	Val	l eu	G] v	Leu	Leu	Val		
1				5					10			-		15			
Leu	Phe	Leu	Thr 20	Cys	Tyr	Ala	Asp	Asp 25	Lys	Pro	Asp	Lys	Pro 30	Asp	Asp ·		
Lys	Pro	Asp 35	Asp	Ser	Gly	Lys	Asp 40		Lys	Pro	Asp	Phe 45		Lys	Phe		
Leu	Ser 50	Leu	Leu	Gly	Thr	G1u 55	Пе	Ile	Glu		Ala 60	Val	Glu	Phe	Ile		
55	Arg				70	Ser	Thr	Gly	Phe			Phe	Asp	Asp	Asn 80		
Glu	Gly	Lys	His	Ser 85	Ser	Lys											
	<2	10>	383														

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<213> Homo sapiens <220> <221> CDS <222> (1)...(225) <400> 383 atg act gcc ctc acc tcc tgg cac ctg gcc tat ctc atc act tgg acc 48 Met Thr Ala Leu Thr Ser Trp His Leu Ala Tyr Leu Ile Thr Trp Thr 1 5 10 15 acc tgc ctg gcc tcc cac ctg ctg cag gct gcc ttt gag cac acg acc 96 Thr Cys Leu Ala Ser His Leu Leu Gln Ala Ala Phe Glu His Thr Thr 20 25 cag ctt gcc gag gcc cag gag gtt gaa ccc cag gag gtc tca ggg tct 144 Gln Leu Ala Glu Ala Gln Glu Val Glu Pro Gln Glu Val Ser Gly Ser 35 40 tcc ttg ctg ccc tca ctg tct gcg tcc tcg gac tca gag tct gga aca 192 Ser Leu Leu Pro Ser Leu Ser Ala Ser Ser Asp Ser Glu Ser Gly Thr 50 55 60 gtt ttg cca gag caa gaa act ccc aga gaa taa 225 Val Leu Pro Glu Gln Glu Thr Pro Arg Glu * 65 70 <210> 384 <211> 74 <212> PRT <213> Homo sapiens <400> 384 Met Thr Ala Leu Thr Ser Trp His Leu Ala Tyr Leu Ile Thr Trp Thr Thr Cys Leu Ala Ser His Leu Leu Gln Ala Ala Phe Glu His Thr Thr 25 Gln Leu Ala Glu Ala Gln Glu Val Glu Pro Gln Glu Val Ser Gly Ser Ser Leu Leu Pro Ser Leu Ser Ala Ser Ser Asp Ser Glu Ser Gly Thr 55 Val Leu Pro Glu Gln Glu Thr Pro Arg Glu 65 70

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<210> 385
      <211> 288
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(288)
      <221> misc feature
      <222> (1)...(288)
      <223> n = A.T.C or G
      <400> 385
atg gcc ccc ccg cnc gcg tnc cgg tcc ccg atg tca ccn cng ncg nng
                                                                       48
Met Ala Pro Pro Xaa Ala Xaa Arg Ser Pro Met Ser Xaa Xaa Xaa Xaa
1
                 5
                                     10
ntg ctg ctg ctg ctg ctg ctg agt ctg gcg ctg ctg ggc gcc cgg gcc
                                                                       96
Xaa Leu Leu Leu Leu Leu Ser Leu Ala Leu Leu Gly Ala Arg Ala
             20
                                 25
cgc gcc gag ccc gcc ggg agt gcc gtc ccc gcg cag agc cgc cca tqc
                                                                      144
Arg Ala Glu Pro Ala Gly Ser Ala Val Pro Ala Gln Ser Arg Pro Cys
         35
                             40
gtg gac tgc cac gcc ttc gag ttc atg cag cgc gcc ctg cag gac ctg
                                                                      192
Val Asp Cys His Ala Phe Glu Phe Met Gln Arg Ala Leu Gln Asp Leu
     50
                         55
                                             60
cgg aag aca gcc tgc agc ctg gac gcg cgg acg gag acc cta ctg ctg
                                                                      240
Arg Lys Thr Ala Cys Ser Leu Asp Ala Arg Thr Glu Thr Leu Leu Leu
65
                     70
                                         75
cag gca gag cgc cgt gcc ctg tgt gcc tgc tgg cca gcg ggg cac tga
                                                                      288
Gln Ala Glu Arg Arg Ala Leu Cys Ala Cys Trp Pro Ala Gly His *
                 85
                                     90
                                                         95
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<210> 386

<211> 95

<212> PRT

<213> Homo sapiens

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      <222> (1)...(95)
      <223> Xaa = Any Amino Acid
      <400> 386
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Xaa Leu Leu Leu Leu Leu Ser Leu Ala Leu Leu Gly Ala Arg Ala
Arg Ala Glu Pro Ala Gly Ser Ala Val Pro Ala Gln Ser Arg Pro Cys
Val Asp Cys His Ala Phe Glu Phe Met Gln Arg Ala Leu Gln Asp Leu
                        55
Arg Lys Thr Ala Cys Ser Leu Asp Ala Arg Thr Glu Thr Leu Leu Leu
                                         75
Gln Ala Glu Arg Arg Ala Leu Cys Ala Cys Trp Pro Ala Gly His
                85
                                    90
      <210> 387
      <211> 351
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(351)
      <400> 387
atg aag gga ctc aga agt ctg gca gca aca acc ttg gct ctt ttc ctg
                                                                       48
Met Lys Gly Leu Arg Ser Leu Ala Ala Thr Thr Leu Ala Leu Phe Leu
 1
                                     10
gtg ttt gtt ttc ctg gga aac tcc agc tgc gct ccg cag aga ctg ttg
                                                                       96
Val Phe Val Phe Leu Gly Asn Ser Ser Cys Ala Pro Gln Arg Leu Leu
             20
                                 25
gag aga agg aac tgg act cct caa gct atg ctc tac ctg aaa ggg gca
                                                                      144
Glu Arg Arg Asn Trp Thr Pro Gln Ala Met Leu Tyr Leu Lys Gly Ala
         35
                             40
                                                 45
cag ggt cgc cgc ttc atc tcc gac cag agc cgg aga aag gac ctc tcc
                                                                      192
Gln Gly Arg Arg Phe Ile Ser Asp Gln Ser Arg Arg Lys Asp Leu Ser
```

	50					55					60					
	Arg		ctg Leu												act Thr 80	240
			gca Ala													288
			gaa Glu 100									_	_	_	-	336
			tgg Trp	tga *				•								351
	<2 <2 <2	211> 212> 213>	388 116 PRT Homo	sar	oiens	5										
Met 1			388 Leu	Arg 5	Ser	Leu	Ala	Ala	Thr	Thr	Leu	Ala	Leu	Phe 15	Leu	
_	Phe	Val	Phe 20	_	Gly	Asn	Ser	Ser 25		Ala	Pro	Gln	Arg 30		Leu	
31u	Arg	Arg 35	Asn	Trp	Thr	Pro	G1n 40	Ala	Met	Leu	Tyr	Leu 45	Lys	Gly	Ala	
Gln	G1y 50	Arg	Arg	Phe	Ile	Ser 55	Asp	Gln	Ser	Arg	Arg 60	Lys	Asp	Leu	Ser	
Asp 55	Arg	Pro	Leu	Pro	G1u 70	Arg	Arg	Ser	Pro	Asn 75	Pro	Gln	Leu	Leu	Thr 80	
[le	Pro	Glu	Ala	A1a 85	Thr	Ile	Leu	Leu	A1a 90	Ser	Leu	Gln	Lys	Ser 95	Pro	
	Asp Leu		Glu 100		Asn	Phe	Asp	G1n 105		Arg	Phe	Leu	Glu 110		Ser	
		10> 11>														

524

<212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(318) <400> 389 atg aac ttg ggg gtc agc atg ctg agg atc ctc ttc ctc ctg gat gta 48 Met Asn Leu Gly Val Ser Met Leu Arg Ile Leu Phe Leu Leu Asp Val 10 15 1 96 gga gga gct caa gtg ctg gca aca ggc aag acc cct ggg gct gaa att Gly Gly Ala Gln Val Leu Ala Thr Gly Lys Thr Pro Gly Ala Glu Ile 20 25 30 gat ttc aag tac gcc ctc atc ggg act gct gtg ggt gtc gcc ata tct 144 Asp Phe Lys Tyr Ala Leu Ile Gly Thr Ala Val Gly Val Ala Ile Ser 35 40 gct ggc ttc ctg gcc ctg aag atc tgc atg atc agg agg cac tta ttt 192 Ala Gly Phe Leu Ala Leu Lys Ile Cys Met Ile Arg Arg His Leu Phe 50 55 240 gac gac gac tot too gac otg aaa ago acg oot ggg ggo oto agt gac Asp Asp Ser Ser Asp Leu Lys Ser Thr Pro Gly Gly Leu Ser Asp 65 70 75 80 288 acc atc ccg cta aag aag aga gcc cca agg cga aac cac aat ttc tcc Thr Ile Pro Leu Lys Lys Arg Ala Pro Arg Arg Asn His Asn Phe Ser 95 85 90 318 aaa aga gat gca cag gtg att gag ctg tag Lys Arg Asp Ala Gln Val Ile Glu Leu * 105 100

<210> 390

<211> 105

<212> PRT

<213> Homo sapiens

<400> 390

Met Asn Leu Gly Val Ser Met Leu Arg Ile Leu Phe Leu Leu Asp Val

1				5					10					15		
Gly	Gly	Ala	G1n 20	Val	Leu	Ala	Thr	Gly 25	Lys	Thr	Pro	Gly	A1 a 30		Ile	
Asp	Phe	Lys 35	Tyr	Ala	Leu	Ile	Gly 40	Thr	Ala	Val	Gly	Va1 45	Ala	He	Ser	
Ala	G1y 50	Phe	Leu	Ala	Leu	Lys 55	Ile	Cys	Met	Пe	Arg 60	Arg	His	Leu	Phe	
Asp 65	Asp	Asp	Ser	Ser	Asp 70	Leu	Lys	Ser	Thr	Pro 75	Gly	Gly	Leu	Ser	Asp 80	
Thr	Ile	Pro	Leu	Lys 85	Lys	Arg	Ala	Pro	Arg 90	Arg	Asn	His	Asn	Phe 95	Ser	
Lys	Arg	Asp	Ala 100	Gln	Val	Ile	Glu	Leu 105								
		212>	150 Dna	o sap	oiens	5										,
	<2	220> 221> 222>	CDS (1)	(]	150)											
	<2	222>	(1)	(1	ature 150) ,C or											
	gcc		ctc		gtc Val											48
					gtc Val											96
					cct Pro											144
gcc Ala	taa *															150

526

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527

Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His 50 55 60 tca gcc acc ctg gcg cct att ggc tct cgg ggg cca cag ctg ctc ctg 240 Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu 70 75 cgc ctg ggc ctt act tcc tgc cga gtt cta tgt cca gtg cag cct gac 288 Arg Leu Gly Leu Thr Ser Cys Arg Val Leu Cys Pro Val Gln Pro Asp 95 294 ttc tga Phe *

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 10
 15

 Pro Gln Glu Gln Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg 20
 25
 30

 Pro Leu Pro Gly Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg 35
 40
 45

 Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His 50
 55
 60

 Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu 65
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 Arg Leu Gly Leu Thr Ser Cys Arg Val Leu Cys Pro Val Gln Pro Asp 85
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528

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40

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Lys Asn Leu Glu Asn His Gln Phe Pro Ala Lys Pro Leu Arg Glu Ser
                       55
Gln Ser His Leu Leu Thr Asp Ser Gln Ser Trp Thr Glu Ser Ser Ile
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Glu Asn Glu Thr
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ctc cga gcc ctg tcc atc ttc tcc ctg ttg gcc aac atc acc atg ctg
                                                                  96
Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu
            20
                               25
                                                  30
gtc agc ttg gtc atg atc tac cag ttc att gtt cag atc ctg tga
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Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu *
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                                              45
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Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu
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gga aat ccc act ctg ggc aac tta gcc agc gca ata cgg gaa gag ctg Gly Asn Pro Thr Leu Gly Asn Leu Ala Ser Ala Ile Arg Glu Glu Leu 35 40 45	144
aac ggg gca atg gag cat acc aac agc aac gag agt gac agc agt cca Asn Gly Ala Met Glu His Thr Asn Ser Asn Glu Ser Asp Ser Ser Pro 50 55 60	192
ggc aga tct cct atg caa gcc gtg cat cct gta cac gtc aaa gaa gag Gly Arg Ser Pro Met Gln Ala Val His Pro Val His Val Lys Glu Glu 65 70 75 80	240
ccc ctc gat cca gag gaa gct gaa ggg ccc ctg tcc tta gtg aca aca Pro Leu Asp Pro Glu Glu Ala Glu Gly Pro Leu Ser Leu Val Thr Thr 85 90 95	288
gcc aac cac agt cca gat ttt gac cat gac aga gat tac gaa gat gaa Ala Asn His Ser Pro Asp Phe Asp His Asp Arg Asp Tyr Glu Asp Glu 100 105 110	336
cca gta aac gag gac atg gag tga Pro Val Asn Glu Asp Met Glu * 115	360

531

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						aaa Lys 55										192
						cat His										240
		-				aat Asn				-			-			288
						gct Ala					_	_	-			336
				_		aat Asn			_						-	384
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Ser	Leu		Leu 20	Leu	Leu	Val	Val	Cys 25	Gly	Ile	Gly	Cys	Val 30	Trp	His	
Trp				Val	Ala	Thr	Arg 40		Thr	Leu	Pro	Arg 45		Leu	Gln	
Arg			Ser	Arg	Arg	Lys 55		Cys	Thr	Lys	Thr 60		Leu	Gly	Pro	

533

Arg Ile Ile Gly Leu Arg His Glu Ile Ser Val Glu Thr Gln Asp His 65 70 75 Lys Ser Ala Val Arg Gly Asn Asn Thr His Asp Asn Tyr Glu Asn Val 90 Glu Ala Gly Pro Pro Lys Ala Lys Gly Lys Thr Asp Lys Glu Leu Tyr 105 Glu Asn Thr Gly Gln Ser Asn Phe Glu Glu His Ile Tyr Gly Asn Glu 115 120 125 Thr Ser Ser Asp Tyr Tyr Asn Phe Gln Lys Pro Arg Pro Ser Glu Val 130 135 140 Pro Gln Asp Glu Asp Ile Tyr Ile Leu Pro Asp Ser Tyr 145 150 155 <210> 403 <211> 279 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(279) <400> 403 48 atg tgg cct gtg ttt tgg acc gtg gtt cgt acc tat gct cct tat gtc Met Trp Pro Val Phe Trp Thr Val Val Arg Thr Tyr Ala Pro Tyr Val 1 5 10 15 aca ttc cct gtt gcc ttc gtg gtc ggg gct gtg ggt tac cac ctg gaa 96 Thr Phe Pro Val Ala Phe Val Val Gly Ala Val Gly Tyr His Leu Glu 20 25 30 tgg ttc atc agg gga aag gac ccc cag ccc gtg gag gag gaa aag agc 144 Trp Phe Ile Arg Gly Lys Asp Pro Gln Pro Val Glu Glu Glu Lys Ser 35 atc tca gag cgc cgg gag gat cgc aag ctg gat gag ctt cta ggc aag 192 Ile Ser Glu Arg Arg Glu Asp Arg Lys Leu Asp Glu Leu Leu Gly Lys 50 55 60 gac cac acg cag gtg gtg agc ctt aag gac aag cta gaa ttt gcc ccg 240 Asp His Thr Gln Val Val Ser Leu Lys Asp Lys Leu Glu Phe Ala Pro 65 70 75 aaa gct gtg ctg aac aga aac cgc cca gag aag aat taa 279

534

Lys Ala Val Leu Asn Arg Asn Arg Pro Glu Lys Asn * 85 90

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<211> 92

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Thr Phe Pro Val Ala Phe Val Val Gly Ala Val Gly Tyr His Leu Glu 20 25 30

Trp Phe Ile Arg Gly Lys Asp Pro Gln Pro Val Glu Glu Glu Lys Ser 35 40 45

Ile Ser Glu Arg Arg Glu Asp Arg Lys Leu Asp Glu Leu Leu Gly Lys 50 55 60

Asp His Thr Gln Val Val Ser Leu Lys Asp Lys Leu Glu Phe Ala Pro 65 70 75 80

Lys Ala Val Leu Asn Arg Asn Arg Pro Glu Lys Asn 85 90

Q Q

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Met Ser Glu Phe Trp Leu Cys Phe Asn Cys Cys Ile Ala Glu Gln Pro

1 5 10 15

cag cct aaa agg cga cgg cgg att gac aga agt atg att gga gag ccc
Gln Pro Lys Arg Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro
20 25 30

aca aac ttt gtg cat aca gct cat gtt gga tca gga gac ctg ttc agt 144 Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser 35 40 45

535

gga atg aat toa gtt agc too att cag aac caa atg cag too aag gga 192 Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly 55 50 ggt tat gga ggt gga atg cct gcc aat gtc cag atg cag ctc gtg gat 240 Gly Tyr Gly Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp 75 70 65 80 acg aag gcg gga tag 255 Thr Lys Ala Gly * <210> 406 <211> 84 <212> PRT <213> Homo sapiens <400> 406 Met Ser Glu Phe Trp Leu Cys Phe Asn Cys Cys Ile Ala Glu Gln Pro Gln Pro Lys Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly 55 Gly Tyr Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp 65 70 75 80 Thr Lys Ala Gly <210> 407 <211> 249 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(249) <400> 407 48

536

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	ctg Leu														tca Ser	. 96
_	att Ile	-									-			-	-	144
	ctt Leu 50	_	_							_			_	-		192
-	gag G1u		-	_	_					_	_	-	-		-	240
	agc Ser	tga *														249
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Arg	Ile	Leu 35		Thr	Gly	Leu	Asp 40		Glu	Thr	Leu	Ser 45		Cys	Val	

Arg Leu Cys Glu Gln Gly Ile Asn Pro Glu Ala Leu Ser Ser Val Ile

Lys Glu Leu Arg Lys Ala Thr Glu Ala Leu Lys Ala Ala Glu Asn Met

60

80

75

55

70

<210> 409

65

Thr Ser

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                 5
                                                          15
ctc ctg ggt gct gcc aca gag aag aga gag aga gtg aag cgg gca gag
                                                                       96
Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
             20
                                 25
                                                     30
act ggc tgt tgc cat cac aca act gag ggc gga cct gga gct cac cgg
                                                                      144
Thr Gly Cys Cys His His Thr Thr Glu Gly Gly Pro Gly Ala His Arg
         35
                             40
ctg agg gtt tga
                                                                      156
Leu Arg Val *
     50
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Met Gln Cys Cys Leu Leu Leu Arg Trp Leu Ala Ser Ala Leu Leu Arg
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Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
Thr Gly Cys Cys His His Thr Thr Glu Gly Gly Pro Gly Ala His Arg
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                            40
                                                45
Leu Arg Val
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					gag Glu										96
					cgc Arg										144
					agg Arg										192
					att Ile 70										240
	Ser	Leu	Arg	Xaa	tna Xaa	Asp	Ser	Asp	Asp	Phe	Trp	Thr			288
					atg Met										336
					ctc Leu										384
gcg	ttg	cac	atc	cta	aag	ttt	gaa	gag	tct	aaa	taa				420

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Ala Leu His Ile Leu Lys Phe Glu Glu Ser Lys *
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Val Met Arg Gly Thr Arg Cys Leu Ala Glu Tyr His Leu Gly Asp Tyr
Gly His Ala Trp Asn Arg Cys Trp Val Leu Asp Arg Val Asp Thr Trp
                        55
Ala Val Val Met Phe Ile Asp Phe Gly Gln Leu Ala Thr Ile Pro Val
Gln Ser Leu Arg Xaa Xaa Asp Ser Asp Asp Phe Trp Thr Ile Pro Pro
                                    90
Leu Thr Gln Pro Phe Met Leu Glu Lys Asp Ile Leu Ser Ser Tyr Glu
                                105
                                                    110
Val Val His Arg Ile Leu Lys Gly Lys Ile Thr Gly Ala Leu Asn Ser
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Ala Leu His Ile Leu Lys Phe Glu Glu Ser Lys
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                        135
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						gtg Val			240
						att Ile		-	288
						tgg Trp			336
						cat His 125			384
						tac Tyr			432
						agc Ser			480
				He		gat Asp			528

	tgt Cys		-		_				Ile						•	576
	agc Ser				-					-	_	-			-	624
	gaa Glu 210											-				672
	gag Glu			_						_	-	_			_	720
	gcc Ala										_					768
-	ggt Gly							-								795
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Leu	Leu	Met	Pro 20	Ala	Val	Ser	Val	G1y 25	Asn	Val	Gly	Gln	Leu 30	Ala	Met	
Asp	Leu	Ile 35		Ser	Thr		Asn 40		Ser	Lys	Ile	Gly 45		Phe	Tyr	
Thr	Asp 50		Leu	Val				Gly	Asn	Asn	Pro 60	. –	Ala	Thr	Thr	
G1u 65	Gly	Asn	Ser				Ser	Ilе	Asn	Ala 75		Val	Tyr	Ser	Leu 80	
	Ser	Arg	-			Ala	Leu	Gln	Leu 90	-	Ser	Пe	Phe	Ile 95		
Tyr	Lys	Ser			Phe	Cys	Glu	Lys		Leu	Ser	Trp	Val		Ser	

			100					105					110				
Ser	Gly	Cys 115	Ala	Arg	Val	He	Val 120	Leu	Ser	Ser	Ser	His 125	Ser	Tyr	Gln		
Arg	Asn 130	Asp	Leu	Gln	Leu	Arg 135	Ser	Thr	Pro	Phe	Arg 140	Tyr	Leu	Leu	Thr		
Pro 145	Ser	Met	Gln	Lys	Ser 150	Val	Gln	Asn	Lys	Ile 155	Lys	Ser	Leu	Asn	Trp 160		
Glu	Glu	Met	Glu	Lys 165	Ser	Arg	Cys	Ile	Pro 170	Glu	Ile	Asp	Asp	Ser 175	Glu		
Phe	Cys	Пe	Arg 180	He	Pro	Gly	Gly	Gly 185	Ile	Thr	Lys	Thr	Leu 190	Tyr	Asp		
Glu	Ser	Cys 195	Ser	Lys	G1u	Пе	G1n 200	Met	Ala	Val	Leu	Leu 205	Lys	Phe	Val		
Ser	G1u 210	Gly	Asp	Asn	Ile	Pro 215	Asp	Ala	Leu	Gly	Leu 220	Val	Glu	Tyr	Leu		
Asn 225	Glu	Trp	Leu	Gln	Ile 230	Leu	Lys	Pro	Leu	Ser 235	Asp	Asp	Pro	Thr	Va1 240		
Ser	Ala	Ser	Arg	Trp 245	Lys	Ile	Pro	Ser	Ser 250	Trp	Arg	Leu	Leu	Phe 255	Gly		
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	ctc Leu			-	_	_			-					-		g	96
	atg Met	-	_				-	-	-							14	14

543

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			Asn					Ser					Leu		ata Ile		144
		Leu										Ile			ctt Leu		192
	gaa Glu					Gly											240
	gat Asp																288
	tca Ser															;	336
ctt Leu	cga Arg	tct Ser 115	cag Gln	gct Ala	gca Ala	gtt Val	aca Thr 120	gaa Glu	att Ile	tct Ser	gaa Glu	gag Glu 125	gat Asp	gac Asp	gca Ala	,	384
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Lys	Glu	Leu 35		G1u	Lys		Pro 40		Leu	Ser	Phe	Gly 45		Ala	Ile		
Leu	His 50		Phe	Ser	Ala			Lys	Lys	Val	Gly 60		Lys	Leu	Leu		
Gln	Glu	Пe	Asn	Lys	Gly		Пe	Asp	Ala	Val		Ser	Leu	Met	Пe		

65					70					75					80	
Asn	Asp	Ser	Phe	Cys 85	Ser	Пe	Glu	Lys	Trp 90	Gln	Glu	Val	Ala	Asn 95	Ile	
Cys	Ser	Gln	Asn 100	Gly	Phe	Asp	Lys	Leu 105	Ser	Asn	Asp	He	Thr 110	Ser	Ile	
Leu	Arg	Ser 115	Gln	Ala	Ala	Val	Thr 120	Glu	Ile	Ser	Glu	Glu 125	Asp	Asp	Ala	
Val	Asn 130	Leu	Met	Glu	His	Val 135	Phe	Trp								
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_		_		ttt Phe	-							-	-			96
	_			tgg Trp		-				_			-	_	_	144
				gca Ala												192
				caa G1n												240
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Pro	Leu	Thr 35	Gly	Trp	Ser	Cys	Glu 40	Thr	Pro	Arg	Ser	G1y 45	Met	Leu	Leu	
Gln	Va1 50	Val	Met	Ala	Val	A1a 55	Asp	Thr	Ser	Ala	Lys 60	Ala	Val	Glu	Thr	
Va1 65	Lys	Lys	Gln	Gln	Gly 70	Glu	Gln	Ile	Cys	Trp 75	Gly	G1 <i>y</i>	Ser	Ser	Ser 80	
Val	Met	Ser	Leu	A1a 85	Thr	Lỵs	Met	Asn	Glu 90	Leu	Met	Glu	Lys			•
	<2 <2 <2 <2	220> 221>	240 DNA Homo	·	oiens	5										
				(?	240)											
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	gtg Val															96
	cct Pro															144
	ggc Gly															192

547

50 55 60

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Met Gln Gly Arg Leu Glu Leu Val Gly Arg Gly Cys Arg Pro Leu Ser 5 1

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Val Pro Glu Asp Thr Val Pro Lys Ser Asp Pro Arg Gly Gly Arg Lys

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